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Description

[0001] The present invention relates to an *in vitro* method for the diagnosis of osteochondrosis in a horse which is not more than 12 months old based on the measurement of the expression level of markers in samples obtained from said horse. The present invention further relates to a use of a kit in said method.

[0002] Osteochondrosis (OC) is a family of orthopedic diseases of the joint affecting rapidly growing animals. OC may occur for example in horses and dogs. OC seriously affects the animals' ability to perform athletically and often represents a personal and economic loss to the owner.

[0003] Several processes are believed to be a starting point for the development of OC, for example, abnormal chondrocyte differentiation, formation of a fragile cartilage, failure of blood supply to growing cartilage, and subchondral bone necrosis. Abnormal chondrocyte differentiation is believed to lead to altered enchondral ossification resulting in irregularities in thickness of the epiphyseal cartilage. This mechanism of dyschondroplasia may affect different joints, particularly the metacarpo- and metatarso-phalangeal joints (fetlock joint), the lateral ridge of the talus or the tibial cochlea in the tibio-tarsal joint (hock joint), and the lateral ridge of the trochlea in femoro-patellar joints (stifle joint).

[0004] The ultimate cause for OC appears to be multifactorial. Possible etiologic factors include skeletal growth rates, nutrition, endocrinologic factors, physical exercise of the animal, biomechanics, and genetic effects.

[0005] The time course of the development of OC lesions seems to be joint dependent. In horses, it has been shown that OC lesions appear rapidly after birth but most of these lesions regress in the following months up to the age of 1 year. OC lesions develop in the hock joint in the first month of life. Followed by a period of regression they seem to be stationary after the fifth month of life. In the stifle joint, this process is more delayed and most OC lesions develop around the fifth month of age, thereafter they can decrease to become stationary at the age of eleven months. OC is currently diagnosed by radiography. However, all possibly affected joints shall be radiographed. Moreover, it is frequent that some unusual localizations are not diagnosed by this technique. Furthermore, radiography is not sensitive enough to detect early lesions affecting only the cartilage. Some lesions can be detected by ultrasound but often some parts of the joint are not accessible by echography. Therefore there is a need for another approach for the diagnosis of OC.

[0006] It is known that OC is associated with changes in the transcription profile of a number of genetic markers in leukocytes of horses, which are on average 2.5 years old (Sertejn et al., Journal of Orthopedic research 2010, 28(7): 965-70). For example, it has been shown that the markers ApoB-3G, ISG17, WASH1 and RUSC2 are underexpressed in leukocytes of horses, which are affected by OC and which are on average 2.5 years old, and that the marker Hp is overexpressed in leukocytes of those horses. However, there is so far no information on genetic markers for OC in young animals.

[0007] It is an object of the present invention to provide a minimally-invasive method for the diagnosis of OC in horses which are not more than 12 months old. The method should be able to reliably diagnose OC at a relatively early stage, particularly in young animals. Ideally, the method should be also able to predict the onset of OC in horses which are not more than 12 months old. Furthermore, the method should be able to diagnose which joint is affected by OC.

[0008] In the present disclosure, it has been mentioned that the expression level of certain markers is an indicator for osteochondrosis in terrestrial mammals. In particular, it has been mentioned that the expression level of the marker ApoB3-G is increased in terrestrial mammals affected by osteochondrosis compared to healthy terrestrial mammals of the same species.

[0009] In the present invention, it is provided an *in vitro* method or assay for the diagnosis of osteochondrosis or the prediction of the likelihood of its onset in a horse which is not more than 12 months old, comprising the steps

a) measuring the expression level of a marker in a sample obtained from said horse with an agent that can be used to determine the expression level of said marker, and

b) comparing the expression level measured in step a) to the expression level of said marker measured in a sample obtained from one or more horses not affected by osteochondrosis, characterized in that the marker is ApoB-3G, wherein an increase in the expression level of ApoB-3G is indicative of osteochondrosis.

[0010] The skilled person understands that the increase or decrease in the expression level of a marker used herein is in comparison with the expression level of the respective marker in healthy terrestrial mammals, or horses which are not more than 12 months old.

[0011] As used herein, a "marker" is a gene or a product of a gene, and the "expression level" is any measure for the degree to which the product of the gene is produced. A "product of a gene" as used herein may be mRNA or protein, or fragments thereof. Further, a "product of a gene" may be also a cDNA obtained from the respective mRNA. The skilled person understands that the wording "an agent that can be used to determine the expression level of said marker" means that the agent is suitable for or adapted for said purpose, and that said agent is specific for the respective marker.

[0012] In alternative embodiments of the present disclosure *in vitro* methods or assays are provided for the diagnosis

of osteochondrosis or the prediction of the likelihood of its onset in a terrestrial mammal, comprising the steps

a) measuring the expression level of a marker in a sample obtained from said terrestrial mammal with an agent that can be used to determine the expression level of said marker, and

b) comparing the expression level measured in step a) to the expression level of said marker measured in a sample obtained from one or more terrestrial mammals of the same species not affected by osteochondrosis, characterized in that the marker is selected from the list consisting of *cdh1*, *pcolce2*, *tcf4*, *src*, *sdcl*, *mhc1* and *gja1*, wherein a change in the expression level of the respective maker compared to healthy terrestrial mammal is indicative of osteochondrosis.

[0013] Further described in this application is the measuring of the expression level of the marker "ApoB-3G" replaced by the measuring of the expression level of any one of the following markers: *cdh1*, *pcolce2*, *tcf4*, *src*, *sdcl*, *mhc1* and *gja1*. This means that in a first alternative embodiment the measuring of the expression level of the marker "ApoB-3G" may be replaced by the measuring of the expression level of the marker *cdh1*. In a second alternative the measuring of the expression level of the marker "ApoB-3G" may be replaced by the measuring of the expression level of the marker *pcolce2*. In a third alternative the measuring of the expression level of the marker "ApoB-3G" may be replaced by the measuring of the expression level of the marker *tcf4*. In a fourth alternative the measuring of the expression level of the marker "ApoB-3G" may be replaced by the measuring of the expression level of the marker *src*. In a fifth alternative the measuring of the expression level of the marker "ApoB-3G" may be replaced by the measuring of the expression level of the marker *sdcl*. In a sixth alternative the measuring of the expression level of the marker "ApoB-3G" may be replaced by the measuring of the expression level of the marker *mhc1*. In a seventh alternative the measuring of the expression level of the marker "ApoB-3G" may be replaced by the measuring of the expression level of the marker *gja1*.

[0014] For the purpose of the present invention, a "sample" is any sampling of cells, tissues, or body fluids, in which the expression level of a marker can be determined. Examples of such samples include blood, lymph, urine, biopsies, or bone marrow. Samples may be obtained from a subject by various techniques, for example, by scraping a body area or by using a needle to aspirate a body fluid. Preferably, the sample is obtained in a non-invasive or minimally invasive manner.

[0015] In a preferred embodiment of the inventive method, the sample is a blood sample, which can be whole blood, blood serum or plasma.

[0016] The expression level may be determined by measuring, for example, the amount of mRNA or the amount of protein present in the sample. The expression level of the marker can be determined, for example, with an assay for global gene expression in a sample (e.g. using a microarray for gene expression profiling analysis), or by specific detection, for example by quantitative PCR, real time quantitative PCR, or Western blot. In particular, the measurement of the expression level of a marker in a sample obtained from said terrestrial mammal or horse which is not more than 12 months old will be carried out with an agent that can be used to determine the expression level of said marker. Said agent may be primers or primer sets to specifically reverse transcribe and amplify the mRNA of the respective marker or antibody specifically detecting the marker in its protein form, i.e. the marker as a protein.

[0017] That is, in a preferred embodiment, the expression level of a given marker is determined by isolating mRNA from a blood sample obtained from a subject, reverse-transcribing the mRNA into cDNA, and quantifying the amount of cDNA specific for the marker by PCR-based techniques. To account for the variance in the total amount of mRNA in a given sample compared to other samples, the amount of cDNA for a specific marker is normalized to the amount of cDNA for a housekeeping gene. Suitable housekeeping genes for this purpose are those, whose expression level do not differ between subjects affected by osteochondrosis and healthy subjects. Examples for housekeeping genes are *Axin1*, *CtBP1*, and *CD44*.

[0018] In another preferred embodiment the expression level of a given marker is determined by isolating protein from a blood sample obtained from a subject, and quantifying the amount of protein specific for the marker by detection of said protein with a specific antibody, for example, by Western blot. To account for the variance in the total amount of protein in a given sample compared to other samples, the amount of protein for a specific marker is normalized to the amount of protein for a housekeeping gene, such as those mentioned above.

[0019] The expression level in the sample to be studied is compared to a reference value, which is the expression level found in a sample from a subject of the same species not affected by osteochondrosis. Preferably, the reference value is the average expression level found in samples from a population of subjects of the same species not affected by osteochondrosis. Preferably, the average expression level found in samples from a population of subjects of the same species is determined once and then stored in a database for reference. Preferably, the reference value is measured in samples obtained from one or more subjects of the same species and the same age group as the subject, in which osteochondrosis is to be diagnosed.

[0020] The expression level found in the sample is considered to be increased or decreased if the difference of this expression level to the reference value is statistically significant. If the difference is not considered statistically significant,

the expression level is considered unchanged. The difference may be considered to be statistically significant if its absolute value exceeds a predetermined threshold value. This threshold value can, for example, be the standard deviation of the expression level found in samples from a population of subjects not affected by osteochondrosis as indicated in table 2 and figure 2. For example, in case the method of qPCR is used, the data obtained are analyzed using the 2(-Delta Delta C(T)) ($\Delta\Delta C_t$) method (Livak, KJ and Schmittgen TD, Methods, 2001 Dec.; 25 (4); pages 402-408). The ΔC_t values are determined for all target genes by subtracting the C_t values from the mean of the C_t values of the reference (house-keeping) genes. Values are indicated in table 2 and figure 2.

[0021] In addition to ApoB-3G, it has also been found that the expression levels of each of the markers Dsh1, Foxl1, Hp, ISG17, Mark2, PPP2R1A-a, PPP2R1A-b, RUSC2 and WASH1 are indicative of osteochondrosis. Hence, the present invention also provides a method, in which the expression levels of one or more of these markers are measured in addition to the expression level of ApoB-3G. The expression level of each individual marker is compared to the expression level of said marker in subjects not affected by osteochondrosis. In this method osteochondrosis is indicated by a decrease in the expression levels of Dsh1, Foxl1, Hp, ISG17, Mark2 and/or RUSC2, and/or an increase or decrease in the expression level of PPP2R1A-a, PPP2R1A-b and/or WASH1.

[0022] The reliability of the inventive method will increase with the number of markers investigated. Hence, in addition to measuring the expression level of ApoB-3G, the method preferably comprises measuring the expression levels of at least one, preferably two, three, four, five, six, seven, eight and most preferably all of said additional markers Dsh1, Foxl1, Hp, ISG17, Mark2, PPP2R1A-a, PPP2R1A-b, RUSC2 and WASH1.

[0023] In a particularly preferred embodiment, the method comprises measuring the expression levels of the markers ApoB-3G, Dsh1, Foxl1, Hp, PPP2R1A-a, RUSC2 and WASH1. In an even more preferred embodiment, the method comprises measuring the expression levels of the markers ApoB-3G, Dsh1, Foxl1, Hp, ISG17, Mark2, PPP2R1A-a, PPP2R1A-b, RUSC2 and WASH1.

[0024] It has further surprisingly been found in the present invention that the pattern of expression levels of the aforementioned markers is an indicator for the joint, which is affected by osteochondrosis. The present invention therefore also provides an *in vitro* method or assay wherein the expression levels of at least one, two, several or all of the additional markers Dsh1, Foxl1, Hp, PPP2R1A-a, RUSC2 and WASH1 are measured, wherein the expression levels of Dsh1, Foxl1, Hp, PPP2R1A-a, RUSC2 and WASH1 are further used to diagnose and/or predict whether the fetlock joint, the hock joint or the stifle joint is or will be affected by osteochondrosis. In a particularly preferred method the expression levels of at least the markers of one of the following marker combinations are measured: Foxl1 and WASH1; or Foxl1 and PPP2R1A-a.

[0025] The joints, which can be preferably distinguished with the inventive method are the metacarpo- and metatarso-phalangeal joint (fetlock joint), the tibio-tarsal joint (hock joint) and the femoro-patellar joint (stifle joint).

[0026] In another preferred embodiment of the present invention the expression levels of at least one, two, several or all of the additional markers Dsh1, Foxl1, Hp, PPP2R1A-a, RUSC2 and WASH1, are measured, an increase in the expression level of each PPP2R1A-a and WASH1, a decrease in the expression level of each Dsh1, Foxl1, Hp and RUSC2 is indicative of affection of the fetlock joint;

a decrease in the expression level of each Dsh1, Hp, PPP2R1A-a, RUSC2 and WASH1 and no change in the expression level of Foxl1 is indicative of affection of the hock joint; and

a decrease in the expression level of each Dsh1, Foxl1, Hp, PPP2R1A-a, RUSC2 and WASH1 is indicative of affection of the stifle joint. In a particularly preferred method the expression levels of at least the markers of one of the following marker combinations are measured: Foxl1 and WASH1; or Foxl1 and PPP2R1A-a.

[0027] In a further preferred embodiment of the method of the present invention the expression levels of at least one, two, several or all of the additional markers Dsh1, Foxl1, Hp, Mark2, PPP2R1A-a, WASH1, ISG17, PPP2R1A-b and RUSC2 are measured, wherein the expression levels of Dsh1, Foxl1, Hp, Mark2, PPP2R1A-a, WASH1, ISG17, PPP2R1A-b and RUSC2 are further used to diagnose and/or predict whether the fetlock joint, the hock joint or the stifle joint is or will be affected by osteochondrosis. In a particularly preferred method the expression levels of at least the markers of one of the following marker combinations are measured: Foxl1 and WASH1; or Foxl1 and PPP2R1A-a; or Foxl1 and PPP2R1A-b.

[0028] In another preferred embodiment of the present invention the expression levels of at least one, two, several or all of the additional markers Dsh1, Foxl1, Hp, Mark2, PPP2R1A-a, WASH1, ISG17, PPP2R1A-b and RUSC2 are measured, wherein an increase in the expression level of each PPP2R1A-a, PPP2R1A-b and WASH1, a decrease in the expression level of each Dsh1, Foxl1, Hp, Mark2 and RUSC2 and no change in the expression level of ISG17 is indicative of affection of the fetlock joint;

a decrease in the expression level of each Dsh1, Hp, ISG17, Mark2, PPP2R1A-a, PPP2R1A-b, RUSC2 and WASH1 and no change in the expression level of Foxl1 is indicative of affection of the hock joint; and

a decrease in the expression level of each Dsh1, Foxl1, Hp, ISG17, Mark2, PPP2R1A-a, PPP2R1A-b, RUSC2 and WASH1 is indicative of affection of the stifle joint. In a particularly preferred method the expression levels of at least the markers of one of the following marker combinations are measured: Foxl1 and WASH1; or Foxl1 and PPP2R1A-a; or

Foxl1 and PPP2R1A-b.

[0029] This means that for example the expression level of one of the following markers are measured and further used to diagnose and/or predict whether the fetlock joint, the hock joint or the stifle joint is or will be affected by osteo-
chondrosis: Dsh1, Foxl1, Hp, Mark2, PPP2R1A-a, WASH1, ISG17, PPP2R1A-b and RUSC2. Further, the expression
level of any one of the following sets of markers are measured and further used to diagnose and/or predict whether the
fetlock joint, the hock joint or the stifle joint is or will be affected by osteo-
chondrosis:

Dsh1, Foxl1; Dsh1, Hp; Dsh1, Mark2; Dsh1, PPP2R1A-a; Dsh1, WASH1; Dsh1,
ISG17; Dsh1, PPP2R1A-b; Dsh1, RUSC2; Foxl1, Hp; Foxl1, Mark2; Foxl1,
PPP2R1A-a; Foxl1, WASH1; Foxl1, ISG17; Foxl1, PPP2R1A-b; Foxl1, RUSC2;
Hp, Mark2; Hp, PPP2R1A-a; Hp, WASH1; Hp, ISG17; Hp, PPP2R1A-b; Hp,
RUSC2; Mark2, PPP2R1A-a; Mark2, WASH1; Mark2, ISG17; Mark2, PPP2R1A-
b; Mark2, RUSC2; PPP2R1A-a, WASH1; PPP2R1A-a, ISG17; PPP2R1A-a,
PPP2R1A-b; PPP2R1A-a, RUSC2;
Dsh1, Foxl1, Hp;
Dsh1, Foxl1, RUSC2;
Dsh1, Foxl1, PPP2R1A-a;
Dsh1, Foxl1, WASH1;
Foxl1, Hp, RUSC2;
Foxl1, Hp, PPP2R1A-a;
Foxl1, Hp, WASH1;
Hp, RUSC2, PPP2R1A-a;
Hp, RUSC2, WASH1;
RUSC2, PPP2R1A-a, WASH1;
Dsh1, Foxl1, Hp, RUSC2;
Dsh1, Foxl1, Hp, PPP2R1A-a;
Dsh1, Foxl1, Hp, WASH1;
Foxl1, Hp, RUSC2, PPP2R1A-a;
Foxl1, Hp, RUSC2, WASH1;
Hp, RUSC2, PPP2R1A-a, WASH1;
Dsh1, Foxl1, PPP2R1A-a, WASH1;
Dsh1, Foxl1, RUSC2, WASH1;
Dsh1, Foxl1, RUSC2, PPP2R1A-a;
Dsh1, Foxl1, Hp, WASH1;
Dsh1, Foxl1, Hp, PPP2R1A-a;
Dsh1, RUSC2, PPP2R1A-a, WASH1;
Dsh1, Foxl1, Hp, WASH1;
Dsh1, Hp, PPP2R1A-a, WASH1;
Dsh1, Hp, RUSC2, WASH1;
Dsh1, Hp, RUSC2, PPP2R1A-a;
Dsh1, Hp, RUSC2, WASH1;
Dsh1, Hp, RUSC2, PPP2R1A-a;
Dsh1, Foxl1, Hp, RUSC2, PPP2R1A-a;
Dsh1, Foxl1, Hp, RUSC2, WASH1;
Dsh1, Foxl1, Hp, PPP2R1A-a, WASH1;
Dsh1, Foxl1, RUSC2, PPP2R1A-a, WASH1;
Dsh1, Hp, RUSC2, PPP2R1A-a, WASH1;
Foxl1, Hp, RUSC2, PPP2R1A-a, WASH1;
Dsh1, Foxl1, Hp, RUSC2, PPP2R1A-a, WASH1.

It is particularly preferred that the expression levels of at least the markers of one of the following marker combinations are measured:

Foxl1, WASH1; or
Foxl1, PPP2R1A-a; or
Foxl1, PPP2R1A-b.

[0030] In another preferred embodiment of the present invention the expression levels of the additional markers Dsh1,

Foxl1, Hp, PPP2R1A-a, RUSC2 and WASH1 are measured, wherein

a decrease in the expression level of each Dsh1, Foxl1, Hp, PPP2R1A-a, RUSC2 and WASH1 is indicative of affection of the stifle joint.

[0031] In a further preferred embodiment of the present invention the expression levels of the additional markers Dsh1, Foxl1, Hp, ISG17, Mark2, PPP2R1A-a, PPP2R1A-b, RUSC2 and WASH1 are measured, wherein a decrease in the expression level of each Dsh1, Foxl1, Hp, ISG17, Mark2, PPP2R1A-a, PPP2R1A-b, RUSC2 and WASH1 is indicative of affection of the stifle joint.

[0032] In a particularly preferred embodiment the expression levels of any one or more or all of the following markers are measured and further used to diagnose and/or predict whether the fetlock joint, the hock joint or the stifle joint is or will be affected by osteochondrosis; wherein the degree of expression of the respective marker as given in the following table compared to the normal expression indicates which joint is or will be affected by osteochondrosis:

	fetlock	hock	stifle
	expression level in % compared to normal expression level		
Dsh 1	90-50%	90-50%	< 50%
Foxl1	< 80%	120-80%	< 80%
Hp	80-20%	<20%	80-20%
ISG17	130-70%	< 50%	< 50%
Mark2	90-60%	90-60%	< 60%
PPP2R1A-a	>110%	90-30%	< 30%
PPP2R1A-b	>110%	90-30%	< 30%
RUSC2	90-40%	< 40%	< 40%
WASH1	>110%	90-60%	< 60%

[0033] The method of the present disclosure is used for the diagnosis of osteochondrosis in terrestrial mammals, preferably in terrestrial mammals of the order of Carnivora, Artiodactyla, and Perissodactyla.

The method of the present invention is used for the diagnosis of osteochondrosis for horse, particularly preferred *Equus sp.*, most preferred *Equus caballus*.

[0034] The method of the present invention can be used to diagnose osteochondrosis at a very early stage. Preferably the method of the present invention is used to predict osteochondrosis at a stage, at which it is not possible to reliably diagnose osteochondrosis by other methods known in the art, for example by radiography. The method of the present invention therefore offers the possibility of predicting the likelihood of the onset of osteochondrosis as well.

[0035] Preferably, the method is used for the diagnosis of osteochondrosis in young subjects. In the context of the present invention, a "young" animal is an animal that has not yet reached sexual maturity. Preferably, a "young" animal is an animal which is still growing rapidly. As an example and particularly preferred embodiment, the inventive method can be used to diagnose osteochondrosis in a horse (genus *Equus*, preferably *Equus caballus*), which is not more than twelve months old.

[0036] The present invention therefore provides a method for the diagnosis of osteochondrosis in a horse (genus *Equus*, preferably *Equus caballus*), which is not more than twelve months old, by measuring the expression level of the marker ApoB-3G, wherein an increase in the expression level of ApoB-3G is indicative of osteochondrosis. As mentioned before, the step of measuring the expression level of ApoB-3G may be replaced by measuring the expression level of any of cdh1, pcolce2, tcf4, src, sdc1, mhc1 and gja1.

[0037] In a preferred embodiment the present invention provides a method for the diagnosis of osteochondrosis in a horse (genus *Equus*, preferably *Equus caballus*), which is not more than twelve months old, by additionally measuring the expression level of at least one of the markers Dsh1, Foxl1, Hp, ISG17, Mark2, PPP2R1A-a, PPP2R1A-b, RUSC2 and WASH1, wherein osteochondrosis is indicated by a decrease in the expression levels of Dsh1, Foxl1, Hp, ISG17, Mark2, and/or RUSC2, and/or an increase or decrease in the expression level of PPP2R1A-a, PPP2R1A-b and/or WASH1.

[0038] In another preferred embodiment the present invention provides a method for the diagnosis and/or prediction of which joint in a horse (genus *Equus*, preferably *Equus caballus*), which is not more than twelve months old, is or will be affected by osteochondrosis by additionally measuring the expression levels of at least one, two, several or all of the markers Dsh1, Foxl1, Hp, PPP2R1A-a, RUSC2 and WASH1. In this method, an increase in the expression level of each

PPP2R1A-a and WASH1, a decrease in the expression level of each Dsh1, Foxl1, Hp and RUSC2 is indicative of affection of the fetlock joint;

a decrease in the expression level of each Dsh1, Hp, PPP2R1A-a, RUSC2 and WASH1 and no change in the expression level of Foxl1 is indicative of affection of the hock joint; and

a decrease in the expression level of each Dsh1, Foxl1, Hp, PPP2R1A-a, RUSC2 and WASH1 is indicative of affection of the stifle joint.

[0039] In still another preferred embodiment the present invention provides a method for the diagnosis and/or prediction of which joint in a horse (genus *Equus*, preferably *Equus caballus*), which is not more than twelve months old, is or will be affected by osteochondrosis by additionally measuring the expression levels of one or more or all of the markers Dsh1, Foxl1, Hp, Mark2, PPP2R1A-a, WASH1, ISG17, PPP2R1A-b and RUSC2. In this method, an increase in the expression level of each PPP2R1A-a, PPP2R1A-b and WASH1, a decrease in the expression level of each Dsh1, Foxl1, Hp, Mark2 and RUSC2 and no change in the expression level of ISG17 is indicative of affection of the fetlock joint;

a decrease in the expression level of each Dsh1, Hp, ISG17, Mark2, PPP2R1A-a, PPP2R1A-b, RUSC2 and WASH1 and no change in the expression level of Foxl1 is indicative of affection of the hock joint; and

a decrease in the expression level of each Dsh1, Foxl1, Hp, ISG17, Mark2, PPP2R1A-a, PPP2R1A-b, RUSC2 and WASH1 is indicative of affection of the stifle joint.

[0040] The present invention also provides an *in vitro* method or assay for the prediction of the likelihood of the onset of osteochondrosis in a horse which is not more than 12 months old, comprising the steps

a) measuring the expression level of two or more markers in a sample obtained from said horse, and

b) comparing the expression level measured in step a) to the expression level of said marker measured in a sample obtained from one or more horses not affected by osteochondrosis, characterized in that

at least one of the markers is ApoB-3G and the additional marker(s) is/are selected from the list consisting of Dsh1, Foxl1, Hp, ISG17, Mark2, PPP2R1A-a, PPP2R1A-b, RUSC2 and WASH1. In a preferred method the sample is a blood sample, which can be whole blood, blood serum or plasma. In a further preferred method of the present disclosure the terrestrial mammals are selected from the order of Carnivora, Artiodactyla and Perissodactyla. In another preferred method of the present invention the horse is *Equus sp.*, even more preferred *Equus caballus*, and most preferred horse (*Equus sp.*, *Equus caballus*) which is not more than 12 months old.

[0041] The present invention also relates to a use of diagnostic kit in the method described above. This kit facilitates the method comprising the steps of measuring the expression level of a marker in a sample obtained from a terrestrial mammal, and comparing said expression level to the expression level of said marker measured in samples obtained from one or more terrestrial mammals of the same species not affected by osteochondrosis.

[0042] The diagnostic kit comprises at least one agent, which binds specifically to the product of the gene of the respective marker and which can be used to determine the expression level of said marker, wherein the marker is ApoB-3G. The product of a gene of a marker can be, for example, the protein, mRNA or cDNA corresponding to said marker. The diagnostic kit also comprises instructions for use to diagnose osteochondrosis according to method described above.

[0043] In alternative embodiments, the diagnostic kit comprises additional agent(s) each for measuring the expression level of a marker selected from the list consisting of pcolce2, tcf4, src, sdc1, mhc1 and gja1, wherein each additional agent binds specifically to the product of the gene of the respective marker and can be used to determine the expression level of the respective marker.

[0044] The kit optionally comprises additional agent(s) for measuring the expression level of one or more additional markers and/or for measuring the expression levels of one or more housekeeping genes. Said additional markers are suitable for the diagnosis of osteochondrosis or the prediction of the likelihood of its onset in a terrestrial mammal. Alternatively or in addition, said additional markers are suitable for to diagnose and/or predict whether the fetlock joint, the hock joint or the stifle joint is or will be affected by osteochondrosis.

[0045] In a further embodiment, the diagnostic kit further comprises additional agent(s) each for measuring the expression level of a marker selected from the list consisting of Dsh1, Foxl1, Hp, ISG17, Mark2, PPP2R1A-a, PPP2R1A-b, RUSC2 and WASH1, wherein each additional agent binds specifically to the product of the gene of the respective marker and can be used to determine the expression level of the respective marker.

[0046] Preferably, the diagnostic kit also comprises additional agent(s) for measuring the expression level of a housekeeping gene selected from the list consisting of Axin1, CtBP1 and CD44, wherein each additional agent binds specifically to the gene product of the respective housekeeping gene and can be used to determine the expression level of the respective housekeeping gene.

[0047] In a preferred embodiment the agent binds specifically to the protein corresponding to a given marker or housekeeping gene. Preferably, this is a specific antibody to said protein. The antibody may be modified with a detectable label, for example by covalently attaching one or more fluorescent dyes to the antibody. The antibody may also be

detectable by a labeled secondary antibody. Preferably, the diagnostic kit also comprises said labeled secondary antibody.

[0048] As mentioned above, the agent is an antibody which binds specifically to the protein corresponding to a given marker or housekeeping gene. The antibody may be a common antibody (which is composed of two heavy protein chains and two light chains), Fab fragments of a common antibody, single-chain variable fragments or single-domain antibody (sdAb). Said antibody specifically binds to the respective marker, which preferably has one of the amino acid sequences shown in SEQ ID NO: 14 to 23 (table 3); or to a housekeeping marker, which preferably has one of the amino acid sequences shown in SEQ ID NO: 24 to 26 (table 3). Further preferred, the respective antibody specifically recognizes an epitope (a stretch of 5 or more consecutive amino acid residues), within one of the amino acid sequences shown in SEQ ID NO: 14-26.

[0049] Regardless of structure, an antibody fragment binds with the same antigen that is recognized by the full-length antibody, and, in the context of the present invention, methods of making and screening antibody fragments are well-known in the art.

[0050] In another preferred embodiment the agent binds specifically to the mRNA or cDNA corresponding to a given marker. Preferably such an agent is an oligonucleotide primer set suitable for the specific amplification of a complete or partial sequence of the mRNA or cDNA corresponding to a given marker in a polymerase chain reaction. The oligonucleotide primer set may comprise two specific oligonucleotide primers that hybridize to the coding or untranslated region of the mRNA or cDNA. The oligonucleotide primer set may also only include one specific oligonucleotide primer that hybridizes to the coding or 5'-untranslated region or 3'-untranslated region of the mRNA or cDNA and a second unspecific oligonucleotide primer that hybridizes to the polyadenosine or polythymidine region of the mRNA or cDNA, respectively. Said oligonucleotide primers specifically bind to the respective mRNA or cDNA, which preferably has one of nucleotide sequences shown in SEQ ID NO: 1 to 10 (table 3); or to a housekeeping marker, which preferably has one of the nucleotide sequences shown in SEQ ID NO: 11 to 13 (table 3).

[0051] As used herein the term "polyadenosine region" means a portion at the 3'-end of the mRNA consisting of at least 10, 15, 20, 30, 50, 80, 100, 150, 200 or more consecutive adenosine residues.

[0052] As used herein the term "polythymidine region" means a portion of the cDNA, prepared from above mentioned mRNA, located at the 5'-end of the cDNA strand which is complementary to the mRNA from which the cDNA is prepared, and which portion consists of at least 10, 15, 20, 30, 50, 80, 100, 150, 200 or more consecutive thymidine residues.

[0053] Most preferably an oligonucleotide primer set comprises a forward primer with a length of 10 to 40 nucleotides that possesses at least 70% sequence identity with a continuous sequence of the same length selected from the DNA sequence of the respective marker and either a reverse primer with a length of 10 to 40 nucleotides that possesses at least 70% sequence identity with a continuous sequence of the same length selected from the sequence complementary to the DNA sequence of the respective marker, or a reverse primer with a length of 10 to 40 nucleotides that possesses at least 70% sequence identity with a continuous polyadenosine or polythymidine sequence of the same length. The DNA sequences for the individual markers and housekeeping genes are listed under SEQ NO ID: 1 to 13 (table 3). For the purpose of the present invention, each list sequence also comprises its reverse complement.

[0054] For the purpose of this invention, it is defined here that in order to determine the sequence identity of two nucleic acid sequences, the sequences are aligned for optimal comparison purposes. For the purpose of defining the oligonucleotide sequences mentioned above, the alignment should preferably not contain any gaps. The nucleotides at corresponding nucleotide positions are then compared. When a position in the first sequence is occupied by the same nucleotide as the corresponding position in the second sequence, then the molecules are identical at that position. The sequence identity between the two sequences is given in percent and is a function of the number of identical positions shared by the sequences (i.e., % identity=number of identical positions/total number of positions (i.e. overlapping positions)*100). Preferably, the two sequences are the same length.

[0055] The skilled person will be aware of the fact that several different computer programmes are available to determine the homology between two sequences. For instance, a comparison of sequences and determination of percent identity between two sequences can be accomplished using a mathematical algorithm. In a preferred embodiment, the percent identity between two amino acid sequences is determined using the Needleman and Wunsch (J. Mol. Biol. (48): 444-453 (1970)) algorithm which has been incorporated into the GAP program in the GCG software package (available at <http://www.gcg.com>), using either a Blossom 62 matrix or a PAM250 matrix, and a gap weight of 16, 14, 12, 10, 8, 6, or 4 and a length weight of 1, 2, 3, 4, 5, or 6. The skilled person will appreciate that all these different parameters will yield slightly different results but that the overall percentage identity of two sequences is not significantly altered when using different algorithms.

[0056] In yet another embodiment, the percent identity between two nucleotide sequences is determined using the GAP program in the GCG software package (available at <http://www.gcg.com>), using a NWSgapdna. CMP matrix and a gap weight of 40, 50, 60, 70, or 80 and a length weight of 1, 2, 3, 4, 5, or 6. In another embodiment, the percent identity between two nucleotide sequences is determined using the algorithm of E. Meyers and W. Miller (CABIOS, 4:11-17 (1989) which has been incorporated into the ALIGN program (version 2.0) (available at: <http://vega.igh.cnrs.fr/bin/align>

guess.cgi) using a PAM120 weight residue table, a gap length penalty of 12 and a gap penalty of 4.

Brief Description of Figures

[0057]

Figure 1 shows the expression level of ApoB-3G in blood samples from horses affected by osteochondrosis in the fetlock joint, the stifle joint or the hock joint as compared to the control group.

Figure 2: The expression levels of selected markers in blood samples from horses affected by osteochondrosis in the fetlock joint, the stifle joint or the hock joint as compared to the control group.

Modes for carrying out the present invention

[0058] In particular, the present invention provides an *in vitro* method or assay for the diagnosis of osteochondrosis or the prediction of the likelihood of its onset in a horse which is not more than 12 months old, comprising the steps

a) measuring the expression level of a marker in a sample obtained from said horse with an agent that can be used to determine the expression level of said marker, and

b) comparing the expression level measured in step a) to the expression level of said marker measured in a sample obtained from one or more horses not affected by osteochondrosis, characterized in that the marker is ApoB-3G, wherein an increase in the expression level of ApoB-3G is indicative of osteochondrosis.

[0059] In a preferred embodiment the present invention provides a method for the diagnosis and/or prediction of which joint in a horse which is not more than 12 months old (genus *Equus*, preferably *Equus caballus*) is or will be affected by osteochondrosis by additionally measuring the expression levels of the markers Dsh1, Foxl1, Hp, PPP2R1A-a, RUSC2 and WASH1. In this method, an increase in the expression level of each PPP2R1A-a and WASH1, a decrease in the expression level of each Dsh1, Foxl1, Hp and RUSC2 is indicative of affection of the fetlock joint;

a decrease in the expression level of each Dsh1, Hp, PPP2R1A-a, RUSC2 and WASH1 and no change in the expression level of Foxl1 is indicative of affection of the hock joint; and

a decrease in the expression level of each Dsh1, Foxl1, Hp, PPP2R1A-a, RUSC2 and WASH1 is indicative of affection of the stifle joint.

[0060] In a further preferred embodiment the present invention provides a method for the diagnosis and/or prediction of which joint in a horse which is not more than 12 months old (genus *Equus*, preferably *Equus caballus*) is or will be affected by osteochondrosis by additionally measuring the expression levels of the markers Dsh1, Foxl1, Hp, Mark2, PPP2R1A-a, WASH1, ISG17, PPP2R1A-b and RUSC2. In this method, an increase in the expression level of each PPP2R1A-a, PPP2R1A-b and WASH1, a decrease in the expression level of each Dsh1, Foxl1, Hp, Mark2 and RUSC2 and no change in the expression level of ISG17 is indicative of affection of the fetlock joint;

a decrease in the expression level of each Dsh1, Hp, ISG17, Mark2, PPP2R1A-a, PPP2R1A-b, RUSC2 and WASH1 and no change in the expression level of Foxl1 is indicative of affection of the hock joint; and

a decrease in the expression level of each Dsh1, Foxl1, Hp, ISG17, Mark2, PPP2R1A-a, PPP2R1A-b, RUSC2 and WASH1 is indicative of affection of the stifle joint.

[0061] The present invention also provides an *in vitro* method or assay for the prediction of the likelihood of the onset of osteochondrosis in a horse which is not more than 12 months old (genus *Equus*, preferably *Equus caballus*), comprising the steps

a) measuring the expression level of two or more markers in a sample obtained from said horse, and

b) comparing the expression level measured in step a) to the expression level of said marker measured in a sample obtained from one or more horses not affected by osteochondrosis, characterized in that

at least one of the markers is ApoB-3G and the additional marker(s) is/are selected from the list consisting of Dsh1, Foxl1, Hp, ISG17, Mark2, PPP2R1A-a, PPP2R1A-b, RUSC2 and WASH1. In a preferred method the sample is a blood sample, which can be whole blood, blood serum or plasma. In a further preferred method of the present invention the horse is *Equus caballus*.

[0062] The present invention further provides an *in vitro* method or assay for the diagnosis of osteochondrosis or prediction of the likelihood of its onset in a horse (genus *Equus*, preferably *Equus caballus*) which is not more than 12

months old, comprising the steps

a) measuring the expression level of a marker in a sample obtained from said horse with an agent that can be used to determine the expression level of said marker, and

b) comparing the expression level measured in step a) to the expression level of said marker measured in a sample obtained from one or more horses not affected by osteochondrosis;

wherein in step a) and b) the data of one or more or all of the following markers are obtained: Dsh1, Foxl1, Hp, PPP2R1A-a, RUSC2 and WASH1;

c) judging that the fetlock joint, the hock joint or the stifle joint is or will be affected by osteochondrosis from the data:

i) an increase in the expression level of each PPP2R1A-a and WASH1, a decrease in the expression level of each Dsh1, Foxl1, Hp and RUSC2 is indicative of affection of the fetlock joint;

ii) a decrease in the expression level of each Dsh1, Hp, PPP2R1A-a, RUSC2 and WASH1 and no change in the expression level of Foxl1 is indicative of affection of the hock joint; and

iii) a decrease in the expression level of each Dsh1, Foxl1, Hp, PPP2R1A-a, RUSC2 and WASH1 is indicative of affection of the stifle joint.

[0063] In a preferred embodiment the expression level of ApoB-3G is measured, wherein an increase in the expression level of ApoB-3G is indicative of osteochondrosis.

[0064] According to a further preferred embodiment in step a) and b) the data of one or more or all of the following markers are obtained: Dsh1, Foxl1, Hp, Mark2, PPP2R1A-a, WASH1, ISG17, PPP2R1A-b and RUSC2; and step c) is as follows:

c) judging that the fetlock joint, the hock joint or the stifle joint is or will be affected by osteochondrosis from the data:

i) an increase in the expression level of each PPP2R1A-a, PPP2R1A-b and WASH1, a decrease in the expression level of each Dsh1, Foxl1, Hp, Mark2 and RUSC2 and no change in the expression level of ISG17 is indicative of affection of the fetlock joint;

ii) a decrease in the expression level of each Dsh1, Hp, ISG17, Mark2, PPP2R1A-a, PPP2R1A-b, RUSC2 and WASH1 and no change in the expression level of Foxl1 is indicative of affection of the hock joint; and

iii) a decrease in the expression level of each Dsh1, Foxl1, Hp, ISG17, Mark2, PPP2R1A-a, PPP2R1A-b, RUSC2 and WASH1 is indicative of affection of the stifle joint.

[0065] The present invention will be explained in more detail in the following examples which are not limiting the scope of the present invention in any way.

Examples

Diagnosis of osteochondrosis in young horses

[0066] 28 Belgian Warmblood horses with osteochondrosis and 11 Belgian Warmblood horses free of osteochondrosis were included in this study. All horses were no more than 12 months old.

[0067] The horses were checked for osteochondrosis-specific lesions using radiography. All horses were sedated for the radiographic examination using detomidine (0.01 mg/kg IV) alone or combined with butorphanol (0.02 mg/kg IV).

The following views were taken: dorso 60° proximo-palmarodistal oblique and weight bearing lateromedial views of the front feet, lateromedial views of the 4 fetlocks, lateromedial and plantarolateral-dorsomedial oblique views of the hocks and a lateromedial view of the stifles. Horses with palmar or plantar fragmentations of the proximal phalanx were not included in this study. Horses were diagnosed on the basis of characteristic lesions of abnormal endochondral ossification located in the metacarpo and metarso-phalangeal (n = 12), tibiotarsal (n = 4), and femoro-patellar joints (n = 12). Horses with multiple lesions were excluded from the study. Eleven horses without any evidence of osteochondrosis-specific lesions were analyzed as a control group.

[0068] Blood was collected from each horse using the PAXgene blood RNA kit (Qiagen, Courtaboeuf, France). The samples were frozen for later analysis.

[0069] For each sample, total RNA was extracted from 2.5 ml total blood using the PAXgene blood RNA kit (Qiagen, Courtaboeuf, France). The quality of total RNA extracted was checked by capillary electrophoresis analysis using an Agilent BioAnalyser 2100 (Agilent, Palo Alto, CA, USA). RNA quantity was measured using a spectrophotometer NanoDrop ND-1000 (Thermo Scientific, Les Ulis, France). cDNA was synthesized using 700ng of total RNA per sample using the MMLV reverse transcription kit according to the manufacturer's protocol (Invitrogen, Carlsbad, CA).

[0070] Real-time PCR analysis was performed using a 7900HT ABI Prism Real-Time PCR System 384 wells. The reactions were set up using 1 μ l of first cDNA, 3.33 μ M of each primer and 2.5 μ l of SYBR Green (Roche, Basel, Switzerland) in a 4 μ l reaction volume. Cycling conditions were 40 cycles of 95°C for 10 s, 57°C for 20 s, and 72°C for 30s.

[0071] Real-time PCR analysis was performed for each of the markers and housekeeping genes listed in table 1. For each measured marker or housekeeping gene, a cycle threshold value (Ct-value) was obtained (see table 1).

[0072] The expression levels of the markers in horses affected by osteochondrosis and in the control group were compared by calculating $2^{-\Delta\Delta Ct}$ (Schmittgen and Livak, Nature Protocols, 3(6), pages 1101-1108 (2008)). Here, $\Delta Ct = Ct_{\text{Marker}} - Ct_{\text{Housekeeping gene}}$, and $\Delta\Delta Ct = \Delta Ct_{\text{subject}} - \Delta Ct_{\text{Control group}}$. The results of this calculation is given in table 2, figure 1 and figure 2.

[0073] For comparison of the quantitative variables the normality was tested using Shapiro-Wilk, the normality was rejected and a non-parametrical method was used to assert of significant differential gene expression. A Kruskal-Wallis test and a Nemenyi test were used to identify the difference. All statistical tests were performed on the Delta Cycle Threshold (dCt) matrix and using R software v2.14.0. All tests performed were performed with 5% type I (alpha) error.

[0074] The data in table 2, figure 1 and figure 2 demonstrate the expression levels of the markers ApoB-3G, Dsh1, Foxl1, Hp, ISG17, Mark2, PPP2R1A-a, PPP2R1A-b, RUSC2 and WASH1 are indicative of osteochondrosis in young (< 12 months) horses. The data also show that the expression pattern of these markers is indicative of which joint is affected by osteochondrosis. ApoB-3G was found highly overexpressed in blood samples of horses affected by osteochondrosis, regardless of the affected joint (figure 1). Dsh1 was found underexpressed in blood samples of horses affected in the three joints, but especially in the stifle joint. The expression of Foxl1 is normal in horse affected in the hock joint, but this gene is found underexpressed in horses affected in the fetlock joint and the stifle joint. Hp is found underexpressed in fetlock joint and stifle joint affected horses, and is barely detectable in the hock joint affected horses. The expression of ISG17 is unchanged in fetlock joint-affected horses, but this gene is found underexpressed in hock joint and stifle joint-affected horses. The expression profile of Mark2 is basically the same than these of Dsh1/dvl1. PPP2R1A_a and _b share the same expression profile. They are overexpressed in fetlock joint-affected horses, but they were found underexpressed in hock joint and stifle joint affected horses. RUSC2 is slightly underexpressed in fetlock joint-affected horses, and is much more underexpressed in hock joint and stifle joint-affected horses. Finally, Wash1 is found overexpressed in blood samples of fetlock joint-affected horses, but was found underexpressed in hock joint and stifle joint-affected horses.

Table 1: Raw data of the real-time PCR analysis. For each subject, the age and the localization of the osteochondrosis-specific lesion is given ("1" indicates the fetlock joint, "2" the stifle joint, "3" the hock joint, and "4" indicates no lesion, i.e. control group). For each marker or housekeeping gene the measured Ct-value is given.

		markers										housekeeping		
												genes		
Localization	age (months)	RUSC	FoxI1	ISG17	PPP2R1A-b	PPP2R1A-a	Hp	ApoB-3G	WASH1	Mark2	Dsh1	CtBP1	Axin1	CD44
1	10	20.7	19.5	18.3	15.1	15.1	9.6	17.7	17.6	16.0	20.3	10.7	14.0	10.8
1	6	20.0	20.2	17.0	14.9	14.7	20.3	10.8	17.3	15.3	18.8	10.3	13.1	10.1
1	7	21.4	19.6	16.5	16.0	15.6	11.2	17.6	17.9	16.4	19.6	11.5	14.2	11.2
1	8	21.1	21.3	16.1	15.7	15.6	9.6	11.8	17.1	15.6	19.6	10.8	13.9	10.9
1	7	21.1	21.6	17.5	15.4	15.1	21.2	8.2	17.0	16.1	19.8	10.7	13.9	9.7
1	6	20.9	20.0	15.3	15.5	15.5	10.0	6.8	16.8	15.4	19.5	10.7	13.6	10.9
1	6	19.7	20.9	17.0	14.1	14.0	9.9	8.8	16.2	15.0	18.6	9.8	12.9	9.8
1	10	21.4	19.1	15.6	15.0	14.9	21.4	7.8	17.5	15.8	19.3	10.5	13.7	10.4
1	11	20.7	19.8	18.2	15.1	15.0	20.7	10.1	17.1	15.7	19.6	10.5	13.9	10.1
1	6	21.9	19.6	18.5	15.1	15.0	9.6	17.2	17.7	15.6	18.8	10.4	13.7	10.1
1	4	23.1	19.9	17.1	16.3	16.2	21.9	8.6	18.7	16.4	21.6	11.7	14.8	11.4
1	11	20.0	18.9	16.7	14.8	14.6	9.8	15.4	16.9	15.2	19.1	10.4	13.2	10.3
2	11	25.5	19.6	18.5	19.8	21.3	11.6	9.6	19.8	17.5	20.9	11.7	14.5	11.0
2	11	23.0	21.9	21.7	18.3	18.7	11.9	10.6	18.9	17.0	20.2	11.2	14.1	11.0
2	4	24.4	20.4	16.5	17.0	16.8	11.4	16.9	18.7	16.6	22.5	11.3	14.6	11.1
2	5	23.2	20.7	22.7	18.2	18.2	11.6	11.0	19.6	17.0	21.8	10.9	14.1	10.9
2	5	21.2	18.4	19.8	16.8	15.8	9.0	18.4	16.8	14.3	18.2	9.2	12.2	8.6
2	8	25.4	22.3	16.9	18.6	18.8	21.7	13.4	20.7	17.2	22.7	11.8	15.4	11.8
2	7	22.3	20.0	17.1	17.1	16.9	10.8	7.4	18.0	15.9	20.0	10.8	13.8	10.5
2	6	25.7	21.9	22.5	19.0	18.9	11.2	14.0	19.8	17.1	21.1	11.0	14.6	10.9
2	11	21.9	21.1	19.4	17.4	17.3	10.4	9.4	19.4	17.0	21.3	11.7	15.0	11.6
2	1	25.9	19.1	21.9	18.7	18.7	21.7	10.0	20.0	17.1	21.4	12.3	15.5	11.2
2	12	26.5	22.7	20.7	18.9	18.6	21.2	12.7	19.5	17.1	21.9	11.9	15.0	10.9
2	6	23.3	20.2	19.4	16.6	16.6	11.8	8.8	19.1	16.4	22.1	11.4	14.2	10.9

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3	10	21.5	19.3	19.1	15.8	15.9	21.9	10.3	17.7	16.2	19.6	10.6	13.8	10.5
3	6	23.3	19.3	20.1	18.2	17.9	11.8	14.1	18.6	15.9	20.1	11.7	14.7	11.5
3	10	22.7	19.0	18.9	16.6	16.4	9.6	8.2	18.7	16.0	20.0	11.1	14.4	10.5
3	11	23.5	21.3	21.1	17.3	16.9	21.7	9.2	18.6	16.8	21.5	11.5	14.3	11.0
4	9	21.4	20.0	18.2	16.6	16.4	21.1	9.2	18.5	16.8	20.1	11.6	14.6	11.6
4	5	20.7	18.0	16.2	14.8	14.8	9.7	18.0	18.6	15.5	19.6	10.5	14.0	10.3
4	5	21.7	17.9	19.1	16.5	16.1	9.8	16.7	18.1	15.7	20.0	11.6	14.7	10.9
4	4	19.9	19.2	12.9	14.7	14.4	10.7	16.2	16.1	15.0	19.5	10.1	13.3	10.8
4	5	22.6	21.0	13.9	16.4	16.4	23.0	15.6	18.7	16.6	20.3	11.8	14.7	11.8
4	7	23.8	18.4	21.4	18.2	18.2	22.6	12.5	20.1	17.7	19.2	13.2	16.0	12.3
4	9	21.1	20.5	17.0	15.0	15.1	10.1	10.9	18.0	15.6	18.7	10.7	14.1	10.3
4	8	21.4	19.6	18.9	15.6	15.5	10.7	18.9	17.8	15.9	19.8	11.0	14.2	10.9
4	8	21.6	19.3	17.9	16.0	15.9	11.7	13.5	18.5	16.5	20.4	11.5	14.6	11.7
4	10	24.9	20.4	20.7	20.7	a	a	a	a	a	a	a	a	a
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Table 2: Expression of markers in horses affected by osteochondrosis as compared to the control group. An arbitrary value of 1 is given to the expression level in the control group.

	Fetlock	Hock	Stifle	Fetlock	Hock	Stifle
	Mean			Standard Deviation		
ApoB-3G	11.119	26.143	13.929	7.958	16.878	9.085
Dsh1	0.732	0.749	0.347	0.105	0.12	0.064
Foxl1	0.491	1.041	0.483	0.101	0.209	0.143
Hp	0.771	0.016	0.637	0.23	0.028	0.158
ISG17	0.886	0.211	0.237	0.296	0.078	0.128
Mark2	0.732	0.789	0.467	0.138	0.146	0.084
PPP2R1A-a	1.169	0.578	0.193	0.177	0.126	0.04
PPP2R1A-b	1.21	0.503	0.225	0.182	0.149	0.049
RUSC2	0.841	0.31	0.254	0.108	0.053	0.044
WASH1	1.414	0.776	0.467	0.182	0.089	0.066

Table 3: List of markers/housekeeping genes and corresponding SEQ ID NOs.

marker / housekeeping gene	nucleotide sequence	amino acid sequence
	SEQ ID NO.	
ApoB-3G	1	14

(continued)

marker / housekeeping gene	nucleotide sequence	amino acid sequence
	SEQ ID NO.	
Dsh1	2	15
Foxl1	3	16
Hp	4	17
ISG17	5	18
Mark2	6	19
PPP2R1A-a	7	20
PPP2R1A-b	8	21
RUSC2	9	22
WASH1	10	23
Axin1	11	24
CtBP1	12	25
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SEQUENCE LISTING

[0075]

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<120> Method for the Diagnosis of Osteochondrosis

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	cccaagacca gagcagtccc tgggtgtctg acagcccaga gaagactccc actaccagta	720
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30	agtttatgac agccgacgag acacggaacc tgcagaatgt ggacatgaag attgggggtgt	2160
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<400> 14

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20 25 30

10 Leu Pro Asp Gly Asp Ser Arg Val Pro Pro Gly Trp Asp Lys Gly Phe
35 40 45

15 Leu Arg Asn Lys Pro Ile His Met Pro Gly Pro Pro Arg Asp Ala Glu
50 55 60

Met Arg Phe Leu Asp Leu Ile Ser Ser Trp Lys Leu Asp Gln Lys Leu
65 70 75 80

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					165					170					175	
	Met	Glu	Leu	Gln	Arg	Ile	Leu	Gln	Pro	Thr	Glu	Ala	Leu	Val	Leu	Val
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			195					200					205			
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	Arg	Thr	Trp	Pro	Thr	Cys	Leu	His	Val	Arg	Asp	Val	Ser	Ser	Ala	Leu
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	Arg	Gly	Asp	Val	Thr	Cys	Ser	Asn	Val	Phe	Thr	Phe	Leu	Gln	Arg	Ser
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<222> (1)..(1)

<223> Xaa can be any naturally occurring amino acid

<400> 15

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				20					25					30			
	Lys	Asn	Val	Leu	Ser	Asn	Arg	Pro	Val	His	Ala	Tyr	Lys	Phe	Phe	Phe	
10			35					40					45				
	Lys	Ser	Met	Asp	Gln	Asp	Phe	Gly	Val	Val	Lys	Glu	Glu	Ile	Ser	Asp	
		50					55					60					
15	Asp	Asn	Ala	Lys	Leu	Pro	Cys	Phe	Asn	Gly	Arg	Val	Val	Ser	Trp	Leu	
	65					70					75					80	
	Val	Leu	Ala	Glu	Gly	Ala	His	Ser	Asp	Ala	Gly	Ser	Gln	Gly	Thr	Asp	
20					85					90					95		
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25				100					105					110			
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			115					120					125				
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35		145				150					155					160	
	His	Leu	Arg	Gly	Asp	Arg	Arg	Arg	Asp	Leu	Gly	Leu	Pro	Pro	Asp	Ser	
					165					170					175		
40	Thr	Ser	Thr	Val	Leu	Ser	Ser	Glu	Leu	Glu	Ser	Ser	Ser	Phe	Ile	Asp	
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	Arg	Arg	Trp	Pro	Ala	Ile	Glu	Pro	Gly	Asp	Met	Leu	Leu	Ala	Gly	Ala	
10		290					295					300					
	Arg	Val	Ala	Arg	Glu	Leu	Ala	Glu	Gly	Pro	Glu	Leu	Thr	Gln	Ser	Pro	
	305					310					315					320	
15	Ile	Asp	Pro	Ala	Ala	Trp	Val	Ser	His	Thr	Ala	Ala	Leu	Thr	Gly	Ala	
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	Ser	Ser	Ser	Ser	Leu	Thr	Ser	Ser	Val	Pro	Gly	Ala	Ala	Gln	Leu	Glu	
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25	Glu	Ala	Pro	Leu	Thr	Val	Lys	Ser	Asp	Met	Gly	Ala	Ile	Val	Arg	Val	
		370					375					380					
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	Lys	Ile	Thr	Ile	Ala	Asn	Ala	Val	Ile	Gly	Ala	Asp	Val	Val	Asp	Trp	
					405					410					415		
35	Leu	Tyr	Thr	His	Val	Glu	Gly	Phe	Lys	Glu	Arg	Arg	Glu	Ala	Arg	Lys	
				420					425					430			
	Tyr	Ala	Ser	Ser	Met	Leu	Lys	Arg	Gly	Phe	Leu	Arg	His	Thr	Val	Asn	
40			435					440					445				
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		450					455					460					
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		465				470					475					480	
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15	Ser	Gly	Val	Gly	Gly	Ser	Gly	Trp	Arg	Glu	Arg	Pro	Ala	Ser	Gln	Leu
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	Ser	Cys	Gly	Ser	Ser	Pro	Arg	Ser	Gln	Ala	Ser	Ala	Ala	Ala	Pro	Gly
20			595					600					605			
	Leu	Pro	Pro	Leu	His	Pro	Leu	Thr	Lys	Ala	Tyr	Ser	Val	Val	Gly	Gly
25	610						615					620				
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	625					630					635					640
30	Leu	Thr	Gly	Ser	Arg	Gln	Ser	Phe	Gln	Lys	Ala	Met	Gly	Asn	Pro	Cys
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				20					25					30			
	Lys	Pro	Pro	Tyr	Ser	Tyr	Ile	Ala	Leu	Ile	Ala	Met	Ala	Ile	Gln	Asp	
10			35					40					45				
	Ala	Pro	Glu	Gln	Arg	Val	Thr	Leu	Asn	Gly	Ile	Tyr	Gln	Phe	Ile	Met	
		50					55					60					
15	Asp	Arg	Phe	Pro	Phe	Tyr	His	Asp	Asn	Arg	Gln	Gly	Trp	Gln	Asn	Ser	
	65					70					75					80	
	Ile	Arg	His	Asn	Leu	Ser	Leu	Asn	Asp	Cys	Phe	Val	Lys	Val	Pro	Arg	
20				85						90					95		
	Glu	Lys	Gly	Arg	Pro	Gly	Lys	Gly	Ser	Tyr	Trp	Thr	Leu	Asp	Pro	Arg	
25				100					105					110			
	Cys	Leu	Asp	Met	Phe	Glu	Asn	Gly	Asn	Tyr	Arg	Arg	Arg	Lys	Arg	Lys	
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<400> 17

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				20					25					30		
10	Pro	Lys	Pro	Pro	Glu	Ile	Pro	Asn	Gly	Tyr	Val	Glu	His	Leu	Val	Arg
			35					40					45			
15	Tyr	Gln	Cys	Lys	Asn	Tyr	Tyr	Arg	Leu	Arg	Ser	Glu	Gly	Asp	Gly	Val
	50						55					60				
20	Tyr	Ala	Leu	Asn	Ser	Glu	Lys	Gln	Trp	Val	Asn	Lys	Ala	Ser	Gly	Thr
	65					70					75					80
25	Lys	Leu	Pro	Glu	Cys	Glu	Ala	Val	Cys	Gly	Lys	Pro	Lys	Asn	Pro	Val
					85					90					95	
30	Asp	Gln	Val	Gln	Arg	Ile	Ile	Gly	Gly	Leu	Leu	Asp	Ala	Lys	Gly	Ser
				100					105					110		
35	Phe	Pro	Trp	Gln	Ala	Lys	Leu	Val	Ser	Arg	His	Asn	Leu	Thr	Thr	Gly
			115					120					125			
40	Ala	Thr	Leu	Ile	Ser	Glu	Gln	Trp	Leu	Leu	Thr	Thr	Ala	Gln	Asn	Leu
	130						135					140				
45	Phe	Leu	Asn	His	Thr	Pro	Asp	Ala	Lys	Pro	Lys	Asp	Ile	Ala	Pro	Thr
	145					150					155					160
50	Leu	Lys	Leu	Tyr	Val	Gly	Arg	Lys	Gln	Pro	Val	Glu	Ile	Glu	Lys	Val
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5 Val Phe His Pro Asp Tyr Gln Glu Val Asp Ile Gly Leu Ile Lys Leu
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10 Lys Glu Lys Val Pro Val Gly Glu Arg Val Met Pro Ile Cys Leu Pro
195 200 205

15 Ser Lys Asp Tyr Ala Gln Val Gly Arg Val Gly Tyr Val Ser Gly Trp
210 215 220

20 Gly Arg Asn Ala Asn Phe Asn Phe Thr Glu Leu Leu Lys Tyr Val Thr
225 230 235 240

25 Leu Pro Val Ala Asp Gln Asp Thr Cys Val Lys His Tyr Glu Gly Ser
245 250 255

30 Thr Val Pro Glu Lys Lys Thr Asn Arg Ser Ser Val Gly Val Gln Pro
260 265 270

35 Ile Leu Asn Glu His Thr Phe Cys Ala Gly Leu Ser Lys Phe Gln Glu
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40 Asp Thr Cys Tyr Gly Asp Ala Gly Ser Ala Phe Val Ile His Asp Glu
290 295 300

45 Glu Asp Asp Thr Trp Tyr Ala Ala Gly Ile Leu Ser Phe Asp Lys Ser
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<400> 18

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5	Leu	Lys	Asp	Ser	Met	Leu	Val	Ser	Glu	Leu	Lys	Gln	Gln	Ile	Ala	Gln
				20					25					30		
	Lys	Thr	Gly	Val	Pro	Pro	Phe	Gln	Gln	Arg	Leu	Ala	Thr	His	Pro	Ala
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		50					55					60				
15	Pro	Gly	Ser	Thr	Val	Val	Leu	Val	Val	Gln	Asn	Cys	Asp	Thr	Pro	Leu
	65					70					75					80
	Ser	Ile	Leu	Val	Arg	Asn	Gly	Lys	Gly	Arg	Ser	Ser	Ala	Tyr	Glu	Val
20					85					90					95	
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25				100					105					110		
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			115					120					125			
30	Met	Asp	Asp	Gln	Leu	His	Leu	Gly	Glu	Tyr	Glu	Leu	Thr	Ala	Gly	Cys
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5	Asp	Glu	Gln	Pro	His	Ile	Gly	Asn	Tyr	Arg	Leu	Leu	Lys	Thr	Ile	Gly
				20				25						30		
10	Lys	Gly	Asn	Phe	Ala	Lys	Val	Lys	Leu	Ala	Arg	His	Ile	Leu	Thr	Gly
			35					40					45			
15	Lys	Glu	Val	Ala	Val	Lys	Ile	Ile	Asp	Lys	Thr	Gln	Leu	Asn	Ser	Ser
	50						55					60				
20	Ser	Leu	Gln	Lys	Leu	Phe	Arg	Glu	Val	Arg	Ile	Met	Lys	Val	Leu	Asn
	65					70					75					80
25	His	Pro	Asn	Ile	Val	Lys	Leu	Phe	Glu	Val	Ile	Glu	Thr	Glu	Lys	Thr
					85					90					95	
30	Leu	Tyr	Leu	Val	Met	Glu	Tyr	Ala	Ser	Gly	Gly	Glu	Val	Phe	Asp	Tyr
				100					105					110		
35	Leu	Val	Ala	His	Gly	Arg	Met	Lys	Glu	Lys	Glu	Ala	Arg	Ala	Lys	Phe
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	130						135					140				
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	145					150					155					160
10	Ile	Lys	Ile	Ala	Asp	Phe	Gly	Phe	Ser	Asn	Glu	Phe	Thr	Phe	Gly	Asn
					165					170					175	
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15				180					185					190		
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			195					200					205			
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					245					250					255	
30	Leu	Ile	Leu	Asn	Pro	Ser	Lys	Arg	Gly	Thr	Leu	Glu	Gln	Ile	Met	Lys
				260					265					270		
	Asp	Arg	Trp	Met	Asn	Val	Gly	His	Glu	Asp	Asp	Glu	Leu	Lys	Pro	Tyr
35			275					280					285			
	Val	Glu	Pro	Leu	Pro	Asp	Tyr	Lys	Asp	Pro	Arg	Arg	Thr	Glu	Leu	Met
40		290					295					300				
	Val	Ser	Met	Gly	Tyr	Thr	Arg	Glu	Glu	Ile	Gln	Asp	Ser	Leu	Val	Gly
	305					310					315					320
45	Gln	Arg	Tyr	Asn	Glu	Val	Met	Ala	Thr	Tyr	Leu	Leu	Leu	Gly	Tyr	Lys
				325						330					335	
	Ser	Ser	Glu	Leu	Glu	Gly	Asp	Thr	Ile	Thr	Leu	Lys	Pro	Arg	Pro	Pro
50				340					345					350		
	Ala	Asp	Leu	Thr	Asn	Ser	Ser	Ala	Pro	Ser	Pro	Ser	His	Lys	Val	Gln
			355					360					365			
55	Arg	Ser	Val	Ser	Ala	Asn	Pro	Lys	Gln	Arg	Arg	Phe	Ser	Asp	Gln	Ala
	370						375					380				

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	Gly	Pro	Ala	Ile	Pro	Thr	Ser	Asn	Ser	Tyr	Ser	Lys	Lys	Thr	Gln	Ser	385	390	395	400
5	Asn	Asn	Ala	Glu	Asn	Lys	Arg	Pro	Glu	Glu	Asp	Arg	Glu	Ser	Gly	Arg	405	410		415
10	Lys	Ala	Ser	Ser	Thr	Ala	Lys	Val	Pro	Ala	Ser	Pro	Leu	Pro	Gly	Leu	420	425		430
	Glu	Arg	Lys	Lys	Thr	Thr	Pro	Thr	Pro	Ser	Thr	Asn	Ser	Val	Leu	Ser	435	440		445
15	Thr	Ser	Thr	Asn	Arg	Ser	Arg	Asn	Ser	Pro	Leu	Leu	Glu	Arg	Ala	Ser	450	455		460
20	Leu	Gly	Gln	Ala	Ser	Ile	Gln	Asn	Gly	Lys	Asp	Ser	Leu	Thr	Met	Pro	465	470	475	480
	Gly	Ser	Arg	Ala	Ser	Thr	Ala	Ser	Ala	Ser	Ala	Ala	Val	Ser	Ala	Ala	485	490		495
25	Arg	Pro	Arg	Gln	His	Gln	Lys	Ser	Met	Ser	Ala	Ser	Val	His	Pro	Asn	500	505		510
30	Lys	Ala	Thr	Gly	Leu	Pro	Pro	Thr	Asp	Ser	Asn	Cys	Glu	Val	Pro	Arg	515	520		525
35	Pro	Arg	Gln	Val	Thr	Ala	Pro	Gln	Arg	Val	Pro	Val	Ala	Ser	Pro	Ser	530	535		540
	Ala	His	Asn	Ile	Ser	Ser	Ser	Gly	Gly	Ala	Pro	Asp	Arg	Thr	Asn	Phe	545	550	555	560
40	Pro	Arg	Gly	Val	Ser	Ser	Arg	Ser	Thr	Phe	His	Ala	Gly	Gln	Leu	Arg	565	570		575
45	Gln	Val	Arg	Asp	Gln	Gln	Asn	Leu	Pro	Tyr	Gly	Val	Thr	Pro	Ala	Ser	580	585		590
	Pro	Ser	Gly	Asn	Ser	Gln	Gly	Arg	Arg	Gly	Ala	Ser	Gly	Ser	Ile	Phe	595	600		605
50	Ser	Lys	Phe	Thr	Ser	Lys	Phe	Val	Arg	Arg	Asn	Leu	Ser	Phe	Arg	Phe	610	615		620
55	Ala	Arg	Arg	Asn	Leu	Asn	Glu	Pro	Glu	Ser	Lys	Asp	Arg	Val	Glu	Thr	625	630	635	640

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	Leu	Arg	Pro	His	Val	Val	Gly	Ser	Gly	Gly	Asn	Asp	Lys	Glu	Lys	Glu	
					645					650					655		
5	Glu	Phe	Arg	Glu	Ala	Lys	Pro	Arg	Ser	Leu	Arg	Phe	Thr	Trp	Ser	Met	
				660					665					670			
10	Lys	Thr	Thr	Ser	Ser	Met	Glu	Pro	Asn	Glu	Met	Met	Arg	Glu	Ile	Arg	
			675					680					685				
15	Lys	Val	Leu	Asp	Ala	Asn	Ser	Cys	Gln	Ser	Glu	Leu	His	Glu	Lys	Tyr	
		690					695					700					
20	Met	Leu	Leu	Cys	Met	His	Gly	Thr	Pro	Gly	His	Glu	Asn	Phe	Val	Gln	
	705					710					715					720	
25	Trp	Glu	Met	Glu	Val	Cys	Lys	Leu	Pro	Arg	Leu	Ser	Leu	Asn	Gly	Val	
					725					730					735		
30	Arg	Phe	Lys	Arg	Ile	Ser	Gly	Thr	Ser	Met	Ala	Phe	Lys	Asn	Ile	Ala	
				740					745					750			
35	Ser	Lys	Ile	Ala	Asn	Glu	Leu	Lys	Leu								
			755					760									
40	<210> 20																
	<211> 589																
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	<213> Equus caballus																
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	Met	Ala	Ala	Ala	Asp	Gly	Asp	Asp	Ser	Leu	Tyr	Pro	Ile	Ala	Val	Leu
	1				5					10					15	
5	Ile	Asp	Glu	Leu	Arg	Asn	Glu	Asp	Val	Gln	Leu	Arg	Leu	Asn	Ser	Ile
				20					25					30		
10	Lys	Lys	Leu	Ser	Thr	Ile	Ala	Leu	Ala	Leu	Gly	Val	Glu	Arg	Thr	Arg
			35					40					45			
15	Ser	Glu	Leu	Leu	Pro	Phe	Leu	Thr	Asp	Thr	Ile	Tyr	Asp	Glu	Asp	Glu
		50					55					60				
20	Val	Leu	Leu	Ala	Leu	Ala	Glu	Gln	Leu	Gly	Thr	Phe	Thr	Thr	Leu	Val
	65					70					75				80	
25	Gly	Gly	Pro	Glu	Tyr	Val	His	Cys	Leu	Leu	Pro	Pro	Leu	Glu	Ser	Leu
					85					90					95	
30	Ala	Thr	Val	Glu	Glu	Thr	Val	Val	Arg	Asp	Lys	Ala	Val	Glu	Ser	Leu
35																
40																
45																
50																
55																

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[illegible]

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	Phe	Leu	Ala	Gln	Leu	Lys	Asp	Glu	Cys	Pro	Glu	Val	Arg	Leu	Asn	Ile	
	370						375					380					
5	Ile	Ser	Asn	Leu	Asp	Cys	Val	Asn	Glu	Val	Ile	Gly	Ile	Arg	Gln	Leu	
	385					390					395					400	
10	Ser	Gln	Ser	Leu	Leu	Pro	Ala	Ile	Val	Glu	Leu	Ala	Glu	Asp	Ala	Lys	
					405					410					415		
15	Trp	Arg	Val	Arg	Leu	Ala	Ile	Ile	Glu	Tyr	Met	Pro	Leu	Leu	Ala	Gly	
				420					425					430			
20	Gln	Leu	Gly	Val	Glu	Phe	Phe	Asp	Glu	Lys	Leu	Asn	Ser	Leu	Cys	Met	
			435					440					445				
25	Ala	Trp	Leu	Val	Asp	His	Val	Tyr	Ala	Ile	Arg	Glu	Ala	Ala	Thr	Ser	
	450						455					460					
30	Asn	Leu	Lys	Lys	Leu	Val	Glu	Lys	Phe	Gly	Lys	Glu	Trp	Ala	His	Ala	
	465					470					475					480	
35	Thr	Ile	Ile	Pro	Lys	Val	Leu	Ala	Met	Ser	Gly	Asp	Pro	Asn	Tyr	Leu	
					485					490					495		
40	His	Arg	Met	Thr	Thr	Leu	Phe	Cys	Ile	Asn	Val	Leu	Ser	Glu	Val	Cys	
				500					505					510			
45	Gly	Gln	Asp	Ile	Thr	Thr	Lys	His	Met	Leu	Pro	Thr	Val	Leu	Arg	Met	
			515					520					525				
50	Ala	Gly	Asp	Pro	Val	Ala	Asn	Val	Arg	Phe	Asn	Val	Ala	Lys	Ser	Leu	
	530						535					540					
55	Gln	Lys	Ile	Gly	Pro	Ile	Leu	Asp	Asn	Ser	Thr	Leu	Gln	Ser	Glu	Val	
	545					550					555					560	
60	Lys	Pro	Ile	Leu	Glu	Lys	Leu	Thr	Gln	Asp	Gln	Asp	Val	Asp	Val	Lys	
					565					570					575		
65	Tyr	Phe	Ala	Gln	Glu	Ala	Leu	Thr	Val	Leu	Ser	Leu	Ala				
				580					585								

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<211> 589

<212> PRT

<213> Equus caballus

<400> 21

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5	Ile	Asp	Glu	Leu	Arg	Asn	Glu	Asp	Val	Gln	Leu	Arg	Leu	Asn	Ser	Ile	
				20					25					30			
	Lys	Lys	Leu	Ser	Thr	Ile	Ala	Leu	Ala	Leu	Gly	Val	Glu	Arg	Thr	Arg	
10			35					40					45				
	Ser	Glu	Leu	Leu	Pro	Phe	Leu	Thr	Asp	Thr	Ile	Tyr	Asp	Glu	Asp	Glu	
		50					55					60					
15	Val	Leu	Leu	Ala	Leu	Ala	Glu	Gln	Leu	Gly	Thr	Phe	Thr	Thr	Leu	Val	
	65					70					75					80	
	Gly	Gly	Pro	Glu	Tyr	Val	His	Cys	Leu	Leu	Pro	Pro	Leu	Glu	Ser	Leu	
20					85					90					95		
	Ala	Thr	Val	Glu	Glu	Thr	Val	Val	Arg	Asp	Lys	Ala	Val	Glu	Ser	Leu	
				100					105					110			
25	Arg	Ala	Ile	Ser	His	Glu	His	Ser	Pro	Ser	Asp	Leu	Glu	Ala	His	Phe	
			115					120					125				
	Val	Pro	Leu	Val	Lys	Arg	Leu	Ala	Gly	Gly	Asp	Trp	Phe	Thr	Ser	Arg	
30		130					135					140					
	Thr	Ser	Ala	Cys	Gly	Leu	Phe	Ser	Val	Cys	Tyr	Pro	Arg	Val	Ser	Ser	
	145					150					155					160	
35	Ala	Val	Lys	Ala	Glu	Leu	Arg	Gln	Tyr	Phe	Arg	Asn	Leu	Cys	Ser	Asp	
					165					170					175		
	Asp	Thr	Pro	Met	Val	Arg	Arg	Ala	Ala	Ala	Ser	Lys	Leu	Gly	Glu	Phe	
40				180					185					190			
	Ala	Lys	Val	Leu	Glu	Leu	Asp	Asn	Val	Lys	Ser	Glu	Ile	Ile	Pro	Met	
			195					200					205				
45	Phe	Ser	Asn	Leu	Ala	Ser	Asp	Glu	Gln	Asp	Ser	Val	Arg	Leu	Leu	Ala	
		210					215					220					
	Val	Glu	Ala	Cys	Val	Asn	Ile	Ala	Gln	Leu	Leu	Pro	Gln	Glu	Asp	Leu	
50		225				230					235					240	
	Glu	Ala	Leu	Val	Met	Pro	Thr	Leu	Arg	Gln	Ala	Ala	Glu	Asp	Lys	Ser	
					245					250					255		
55	Trp	Arg	Val	Arg	Tyr	Met	Val	Ala	Asp	Lys	Phe	Thr	Glu	Leu	Gln	Lys	

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	260	265	270
5	Ala Val Gly Pro Glu Ile Thr Lys Thr Asp Leu Val Pro Ala Phe Gln 275 280 285		
	Asn Leu Met Lys Asp Cys Glu Ala Glu Val Arg Ala Ala Ala Ser His 290 295 300		
10	Lys Val Lys Glu Phe Cys Glu Asn Leu Ser Ala Asp Cys Arg Glu Asn 305 310 315 320		
15	Val Ile Met Thr Gln Ile Leu Pro Cys Ile Lys Glu Leu Val Ser Asp 325 330 335		
	Ala Asn Gln His Val Lys Ser Ala Leu Ala Ser Val Ile Met Gly Leu 340 345 350		
20	Ser Pro Ile Leu Gly Lys Asp Asn Thr Ile Glu His Leu Leu Pro Leu 355 360 365		
25	Phe Leu Ala Gln Leu Lys Asp Glu Cys Pro Glu Val Arg Leu Asn Ile 370 375 380		
	Ile Ser Asn Leu Asp Cys Val Asn Glu Val Ile Gly Ile Arg Gln Leu 385 390 395 400		
30	Ser Gln Ser Leu Leu Pro Ala Ile Val Glu Leu Ala Glu Asp Ala Lys 405 410 415		
35	Trp Arg Val Arg Leu Ala Ile Ile Glu Tyr Met Pro Leu Leu Ala Gly 420 425 430		
	Gln Leu Gly Val Glu Phe Phe Asp Glu Lys Leu Asn Ser Leu Cys Met 435 440 445		
40	Ala Trp Leu Val Asp His Val Tyr Ala Ile Arg Glu Ala Ala Thr Ser 450 455 460		
45	Asn Leu Lys Lys Leu Val Glu Lys Phe Gly Lys Glu Trp Ala His Ala 465 470 475 480		
	Thr Ile Ile Pro Lys Val Leu Ala Met Ser Gly Asp Pro Asn Tyr Leu 485 490 495		
50	His Arg Met Thr Thr Leu Phe Cys Ile Asn Val Leu Ser Glu Val Cys 500 505 510		
55	Gly Gln Asp Ile Thr Thr Lys His Met Leu Pro Thr Val Leu Arg Met 515 520 525		

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	Ala	Gly	Asp	Pro	Val	Ala	Asn	Val	Arg	Phe	Asn	Val	Ala	Lys	Ser	Leu
	530						535					540				
5	Gln	Lys	Ile	Gly	Pro	Ile	Leu	Asp	Asn	Ser	Thr	Leu	Gln	Ser	Glu	Val
	545					550					555					560
10	Lys	Pro	Ile	Leu	Glu	Lys	Leu	Thr	Gln	Asp	Gln	Asp	Val	Asp	Val	Lys
					565					570					575	
15	Tyr	Phe	Ala	Gln	Glu	Ala	Leu	Thr	Val	Leu	Ser	Leu	Ala			
				580					585							
20	<210> 22 <211> 1511 <212> PRT <213> Equus caballus <400> 22															
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	1				5					10					15	
30	Gly	Glu	Thr	Leu	Ile	Val	His	His	Ile	Pro	Leu	Val	His	Cys	Gln	Val
				20					25					30		
35	Pro	Asp	Arg	Gln	Cys	Arg	Gly	Gly	Ala	Ser	Gly	Gly	Ser	Gly	Ser	Thr
			35					40					45			
40	Arg	Pro	Asn	Pro	Phe	Cys	Pro	Ser	Glu	Leu	Gly	Ile	Thr	Lys	Pro	Asp
	50						55					60				
45	Gln	Asp	Leu	Gly	Gln	Ala	Asp	Ser	Leu	Leu	Tyr	Asn	Ser	Arg	His	Ser
	65					70					75					80
50	Ser	Thr	Gly	Gly	Ser	Ala	Arg	Ser	Ala	Asp	Ser	Thr	Lys	Ser	Arg	Gly
					85					90					95	
55	Arg	Asp	Gly	Arg	Gly	Pro	Gly	Ala	Pro	Lys	Arg	His	Asn	Pro	Phe	Leu
				100					105					110		
60	Gln	Gln	Glu	Gly	Val	Ala	Glu	Pro	Gly	Phe	Gly	Asp	Leu	Tyr	Glu	Asp
			115					120					125			
65	Ser	Ile	Gly	Asp	Ser	Ala	Thr	Gln	Gln	Gln	Ser	Phe	His	Leu	His	Gly
	130						135					140				
70	Ala	Gly	Gln	Pro	Thr	Phe	Gln	Leu	Ser	Ser	Phe	Gln	Leu	Pro	Pro	Thr
	145					150					155					160

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	Gly	Pro	Arg	Val	Gly	Arg	Pro	Trp	Gly	Thr	Arg	Arg	Ser	Arg	Ala	Gly	
					165					170					175		
5	Val	Val	Glu	Gly	Gln	Glu	Gln	Gln	Pro	Val	Thr	Thr	Leu	Asp	Thr	Gln	
				180					185					190			
	Glu	Cys	Ser	Thr	Ser	Tyr	Cys	Cys	Arg	Pro	Glu	Leu	Glu	Ala	Glu	Thr	
10			195					200					205				
	Met	Glu	Leu	Asp	Glu	Cys	Gly	Gly	Pro	Gly	Gly	Ser	Gly	Ser	Gly	Gly	
		210					215					220					
15	Gly	Ala	Ser	Asp	Thr	Ser	Gly	Phe	Ser	Phe	Asp	Gln	Glu	Trp	Lys	Leu	
	225					230					235					240	
	Ser	Ser	Asp	Glu	Ser	Pro	Arg	Asn	Pro	Gly	Cys	Thr	Gly	Ser	Gly	Pro	
20					245					250					255		
	Gln	His	Cys	Arg	Cys	Ser	Ser	Thr	Ser	Ser	Gln	Ser	Glu	Thr	Ala	Asp	
				260					265					270			
25	Gln	Ser	Met	Gly	Tyr	Val	Ser	Asp	Ser	Ser	Cys	Asn	Ser	Ser	Asp	Gly	
			275					280					285				
	Val	Leu	Val	Thr	Phe	Ser	Thr	Leu	Tyr	Asn	Lys	Met	His	Gly	Asn	Ser	
30		290					295					300					
	His	Ala	Asn	Leu	Asn	Ser	Ala	Pro	Gln	Ser	Cys	Ser	Asp	Ser	Ser	Phe	
	305					310					315					320	
35	Cys	Ser	His	Ser	Asp	Pro	Gly	Ala	Phe	Tyr	Leu	Asp	Leu	Gln	Thr	Phe	
					325					330					335		
	Pro	Ala	Glu	Glu	Ser	His	His	Pro	Asn	Asn	Gly	Gly	Arg	Glu	Gly	Gly	
40				340					345					350			
	Tyr	Gly	Cys	Pro	His	Ala	Ser	Ser	Pro	Glu	Leu	Asp	Ala	Asn	Cys	Asn	
			355					360					365				
45	Ser	Tyr	His	Pro	His	Cys	Glu	Pro	Cys	Pro	Ala	Val	Ala	Asp	Leu	Thr	
		370					375					380					
	Ala	Cys	Phe	Gln	Ser	Gln	Ala	Arg	Leu	Val	Val	Ala	Thr	Gln	Asn	Tyr	
50						390					395					400	
	Tyr	Lys	Leu	Val	Thr	Cys	Asp	Leu	Ser	Ser	Gln	Ser	Ser	Pro	Ser	Pro	
					405					410					415		
55	Ala	Gly	Ser	Ser	Ile	Thr	Ser	Cys	Ser	Glu	Glu	His	Thr	Lys	Ile	Ser	

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	420		425		430												
5	Pro	Ala	Pro	Gly	Pro	Gly	Pro	His	Pro	Gly	Pro	Ser	Gln	Pro	Ser	Glu	
			435					440					445				
	Tyr	Tyr	Leu	Phe	Gln	Lys	Pro	Glu	Val	Gln	Pro	Glu	Glu	Gln	Glu	Ala	
		450					455					460					
10	Gly	Gly	Ser	Ser	Glu	Glu	Ala	Ala	Ala	Pro	Val	Gly	Pro	Ala	Met	Ile	
	465					470					475					480	
	Glu	Gly	Gln	Val	Tyr	Thr	Asn	Thr	Ser	Pro	Pro	Asn	Leu	Ser	Thr	Gly	
15					485					490					495		
	Arg	Gln	Arg	Ser	Arg	Ser	Tyr	Asp	Arg	Ser	Leu	Glu	Arg	Ser	Pro	Pro	
				500					505					510			
20	Val	Arg	Leu	Gly	Ser	Leu	Glu	Arg	Met	Leu	Ser	Cys	Pro	Val	Arg	Leu	
			515					520					525				
	Ser	Glu	Gly	Pro	Ala	Ala	Leu	Ala	Gly	Pro	Ser	Ser	Pro	Pro	Arg	Arg	
25		530					535					540					
	Val	Thr	Ser	Phe	Ala	Glu	Leu	Ala	Lys	Gly	Arg	Lys	Lys	Ala	Ala	Gly	
	545					550					555					560	
30	Ser	Gly	Ser	Pro	Pro	Leu	Arg	Val	Ser	Ile	Gly	Asp	Ser	Ser	Gln	Asp	
					565					570					575		
	Phe	Ser	Pro	Ile	Gln	Glu	Thr	Gln	Gln	Asp	Arg	Val	Gly	Pro	Leu	Asp	
35				580					585					590			
	Lys	Gly	Thr	Arg	Cys	Ser	His	Ser	Leu	Pro	Pro	Met	Pro	Leu	Gly	Pro	
			595					600					605				
40	Gly	Met	Asp	Leu	Leu	Asp	Pro	Glu	Pro	Trp	Ser	Thr	Gln	Val	Cys	Gln	
		610					615					620					
	Gly	Pro	Gln	Ser	Ser	Glu	Met	Pro	Ser	Ala	Gly	Leu	Arg	Ala	Ala	Glu	
45		625				630					635					640	
	Gln	Gly	Pro	Leu	Ala	Gln	Leu	Met	Asp	Pro	Gly	Pro	Ala	Leu	Pro	Gly	
50					645					650					655		
	Ser	Pro	Ala	Asn	Ser	His	Pro	Gln	Arg	Asp	Ala	Arg	Ala	Arg	Ala	Asp	
				660					665					670			
55	Gly	Gly	Gly	Ala	Glu	Ser	Arg	Pro	Val	Leu	Arg	Tyr	Ser	Lys	Glu	Gln	
			675					680					685				

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	Arg	Pro	Thr	Thr	Leu	Pro	Ile	Gln	Pro	Phe	Val	Phe	Gln	His	His	Phe	
	690						695					700					
5	Pro	Lys	Gln	Leu	Ala	Lys	Ala	Arg	Ala	Leu	His	Ser	Leu	Ser	Gln	Leu	
	705					710					715					720	
	Tyr	Ser	Leu	Ser	Gly	Cys	Ser	Arg	Ala	Gln	Gln	Pro	Ala	Pro	Leu	Ala	
10					725					730					735		
	Ala	Pro	Thr	Ala	Gln	Val	Pro	Ala	Pro	Ala	Pro	Ser	Gly	Glu	Ser	Gln	
				740					745					750			
15	Ala	Ser	Ala	Asn	Lys	Gly	Ala	Gly	Lys	Ala	Gly	Pro	Glu	Pro	Glu	Thr	
			755					760					765				
	Ser	Arg	Pro	Ser	Pro	Leu	Gly	Ser	Tyr	Ser	Pro	Ile	Arg	Ser	Ala	Gly	
20		770					775					780					
	Pro	Phe	Gly	Pro	Ser	Thr	Asp	Ser	Ser	Pro	Ser	Thr	Ser	Cys	Ser	Pro	
	785					790					795					800	
25	Pro	Leu	Glu	Gln	Ala	Thr	Ala	Thr	Glu	Ser	Pro	Pro	Pro	Trp	Ser	His	
					805					810					815		
	Ser	Cys	Pro	Pro	Ala	Val	Arg	Pro	Ala	Thr	Ser	Gln	Gln	Pro	Pro	Lys	
30				820					825					830			
	Glu	Asp	Gln	Lys	Ile	Leu	Thr	Leu	Ala	Glu	Tyr	Arg	Leu	His	Gly	Thr	
35			835					840					845				
	Gly	Ser	Leu	Pro	Pro	Leu	Gly	Ser	Trp	Arg	Ser	Gly	Phe	Ser	Arg	Ala	
		850					855					860					
40	Glu	Ser	Leu	Ala	Arg	Gly	Gly	Gly	Glu	Gly	Ser	Met	Ala	Ser	Arg	Pro	
	865					870					875					880	
	Ser	Asn	Ala	Asn	His	Leu	Ser	Pro	Gln	Ala	Leu	Lys	Trp	Arg	Glu	Tyr	
45				885						890					895		
	Arg	Arg	Lys	Asn	Pro	Leu	Gly	Pro	Pro	Gly	Leu	Ser	Gly	Ser	Leu	Asp	
				900					905					910			
50	Arg	Arg	Pro	Gln	Glu	Ala	Arg	Leu	Ala	Arg	Arg	Asn	Pro	Ile	Phe	Glu	
			915					920					925				
	Phe	Pro	Gly	Ser	Leu	Ser	Ala	Ala	Gly	His	Leu	Asn	Cys	Arg	Leu	Asn	
55		930					935					940					

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	Gly	Gln	Val	Val	Lys	Pro	Leu	Pro	Leu	Thr	Cys	Pro	Asp	Phe	Gln	Asp	945	950	955	960
5	Pro	Phe	Ser	Leu	Thr	Glu	Lys	Pro	Pro	Ala	Glu	Phe	Cys	Leu	Ser	Pro	965	970	975	
10	Asp	Gly	Asn	Ser	Glu	Ala	Ile	Ser	Ile	Asp	Leu	Leu	Gln	Lys	Lys	Gly	980	985	990	
	Leu	Val	Lys	Ala	Val	Asn	Thr	Ala	Val	Asp	Leu	Ile	Val	Ala	His	Phe	995	1000	1005	
15	Gly	Thr	Ser	Arg	Asp	Pro	Gly	Val	Lys	Ala	Lys	Leu	Gly	Asn	Ser		1010	1015	1020	
20	Ser	Val	Ser	Pro	Asn	Val	Gly	His	Leu	Val	Leu	Lys	Tyr	Leu	Cys		1025	1030	1035	
	Pro	Ala	Val	Arg	Ala	Val	Leu	Glu	Asp	Gly	Leu	Lys	Ala	Phe	Val		1040	1045	1050	
25	Leu	Asp	Val	Ile	Ile	Gly	Gln	Arg	Lys	Asn	Met	Pro	Trp	Ser	Val		1055	1060	1065	
30	Val	Glu	Ala	Ser	Thr	Gln	Leu	Gly	Pro	Ser	Thr	Lys	Val	Leu	His		1070	1075	1080	
35	Gly	Leu	Tyr	Asn	Lys	Val	Ser	Gln	Phe	Pro	Glu	Leu	Thr	Ser	His		1085	1090	1095	
	Thr	Met	Arg	Phe	Asn	Ala	Phe	Ile	Leu	Gly	Leu	Leu	Asn	Ile	Arg		1100	1105	1110	
40	Ser	Leu	Glu	Phe	Trp	Phe	Asn	His	Leu	Tyr	Asn	His	Glu	Asp	Ile		1115	1120	1125	
45	Ile	Gln	Thr	His	Tyr	Gln	Pro	Trp	Gly	Phe	Leu	Ser	Ala	Ala	His		1130	1135	1140	
	Thr	Val	Cys	Pro	Gly	Leu	Phe	Glu	Glu	Leu	Leu	Leu	Leu	Leu	Gln		1145	1150	1155	
50	Pro	Leu	Ala	Leu	Leu	Pro	Phe	Ser	Leu	Asp	Leu	Leu	Phe	Gln	His		1160	1165	1170	
55	Arg	Leu	Leu	Gln	Ser	Gly	Gln	Gln	Gln	Arg	Gln	His	Lys	Glu	Leu		1175	1180	1185	

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	Leu	Arg	Val	Ser	Gln	Asp	Leu	Leu	Leu	Ser	Ala	His	Ser	Thr	Leu
	1190						1195					1200			
5	Gln	Leu	Ala	Gln	Ala	Arg	Gly	Gln	Glu	Gly	Pro	Gly	Asp	Met	Asp
	1205						1210					1215			
10	Arg	Ala	Ala	His	Gly	Glu	Arg	Val	Lys	Gly	Val	Gly	Ala	Pro	Glu
	1220						1225					1230			
	Gly	Gly	Glu	Asp	Glu	Glu	Glu	Glu	Glu	Glu	Thr	Glu	Glu	Met	Ala
	1235						1240					1245			
15	Glu	Ala	Ala	Gly	Gly	Ser	Gly	Arg	Gly	Arg	Trp	Ala	Gln	Gly	Gly
	1250						1255					1260			
20	Gln	Ala	Gly	Trp	Trp	Tyr	Gln	Leu	Met	Gln	Ser	Ser	Gln	Val	Tyr
	1265						1270					1275			
	Ile	Asp	Gly	Ser	Thr	Glu	Gly	Ser	Arg	Phe	Pro	Arg	Gly	Gly	Ser
	1280						1285					1290			
25	Asn	Ser	Ser	Ser	Gly	Ser	Ser	Ser	Glu	Lys	Lys	Lys	Gly	Ala	Gly
	1295						1300					1305			
30	Gly	Arg	Gly	Pro	Pro	Pro	Arg	Glu	Gly	Val	Val	Glu	Gly	Ala	Glu
	1310						1315					1320			
	Ala	Cys	Pro	Ala	Pro	Glu	Glu	Thr	Leu	Gly	Arg	Ala	Trp	Pro	Phe
	1325						1330					1335			
35	Trp	Met	Gly	Ser	Pro	Pro	Asp	Ser	Val	Leu	Ala	Glu	Leu	Arg	Arg
	1340						1345					1350			
40	Ser	Arg	Glu	Arg	Glu	Gly	Ser	Thr	Ala	Pro	Pro	Ala	Glu	Asn	Glu
	1355						1360					1365			
	Glu	Gly	Thr	Ser	Glu	Pro	Ser	Pro	Gly	Gly	Ile	Lys	Trp	Gly	His
	1370						1375					1380			
45	Leu	Phe	Gly	Ser	Arg	Lys	Val	Gln	Arg	Glu	Ala	Arg	Pro	Thr	Asn
	1385						1390					1395			
50	Arg	Leu	Pro	Ser	Asp	Trp	Leu	Ser	Leu	Asp	Lys	Ser	Met	Phe	Gln
	1400						1405					1410			
	Leu	Val	Val	Gln	Thr	Val	Gly	Ala	Arg	Arg	Glu	Pro	Glu	Pro	Arg
	1415						1420					1425			
55	Glu	Ser	Leu	Gln	Glu	Pro	His	Pro	Pro	Ala	Leu	Pro	Ser	Lys	Pro

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	1430		1435		1440
5	Pro Cys Lys Val Lys Ala Leu	Cys His His Leu Ala Thr Gly Pro			
	1445		1450		1455
10	Gly Gln Leu Ser Phe His Lys	Gly Asp Ile Leu Arg Val Leu Gly			
	1460		1465		1470
15	Pro Ala Lys Gly Asp Trp Leu	His Cys Ser Arg Gly Thr Asp Met			
	1475		1480		1485
20	Gly Leu Val Pro Leu Ala Tyr	Val Thr Leu Thr Pro Thr Pro Ser			
	1490		1495		1500
25	Pro Thr Pro Gly Ser Ser Gln	Asn			
	1505		1510		

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<212> PRT

<213> Equus caballus

<400> 23

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	Pro	Pro	Thr	Gly	Thr	Met	Thr	Pro	Thr	Arg	Thr	Gln	His	Ser	Leu	Ala	
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5	Gly	Gln	Thr	Tyr	Met	Val	Pro	Leu	Ile	Gln	Pro	Asp	Leu	Arg	Arg	Glu	
				20					25					30			
	Glu	Ala	Ile	Gln	Gln	Val	Ala	Asp	Ala	Leu	Gln	Tyr	Leu	Gln	Lys	Val	
10			35					40					45				
	Ser	Gly	Asp	Ile	Phe	Ser	Arg	Ile	Ser	Gln	Arg	Val	Glu	Leu	Ser	Arg	
		50					55					60					
15	Ser	Gln	Leu	Gln	Ala	Ile	Gly	Glu	Arg	Val	Ser	Leu	Ala	Gln	Ala	Lys	
	65					70					75					80	
	Ile	Glu	Lys	Ile	Lys	Gly	Ser	Lys	Lys	Ala	Ile	Lys	Val	Phe	Ser	Ser	
20				85						90					95		
	Ala	Lys	Tyr	Pro	Ala	Pro	Glu	Arg	Leu	Gln	Glu	Tyr	Gly	Ser	Ile	Phe	
25				100					105					110			
	Thr	Gly	Ala	Gln	Asp	Pro	Gly	Leu	Gln	Arg	Arg	Pro	Arg	Tyr	Arg	Ile	
			115					120					125				
30	Gln	Ser	Lys	His	Arg	Pro	Leu	Asp	Glu	Arg	Ala	Leu	Gln	Glu	Lys	Leu	
		130					135					140					

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	Lys	Tyr	Phe	Pro	Val	Cys	Val	Asn	Thr	Lys	Leu	Glu	Pro	Glu	Asp	Glu	
	145					150					155					160	
5	Ala	Glu	Glu	Gly	Leu	Gly	Gly	Leu	Pro	Ser	Asn	Ile	Ser	Ser	Val	Ser	
					165					170					175		
10	Ser	Leu	Leu	Leu	Phe	Asn	Thr	Thr	Glu	Asn	Leu	Tyr	Lys	Lys	Tyr	Val	
				180					185					190			
15	Phe	Leu	Asp	Pro	Leu	Ala	Gly	Ala	Val	Thr	Lys	Thr	His	Val	Met	Leu	
			195					200					205				
20	Gly	Ala	Glu	Thr	Glu	Glu	Lys	Leu	Phe	Asp	Ala	Pro	Leu	Ser	Ile	Ser	
		210					215					220					
25	Lys	Arg	Glu	Gln	Leu	Glu	Gln	Gln	Val	Pro	Glu	Asn	Tyr	Phe	Tyr	Val	
	225					230					235					240	
30	Pro	Asp	Leu	Gly	Gln	Val	Pro	Glu	Ile	Asp	Val	Pro	Ser	Tyr	Leu	Pro	
				245						250					255		
35	Asp	Leu	Pro	Gly	Ile	Ala	Asp	Asp	Leu	Met	Tyr	Ser	Ala	Asp	Leu	Gly	
				260					265					270			
40	Pro	Gly	Ile	Ala	Pro	Ser	Ala	Pro	Gly	Thr	Ile	Pro	Glu	Leu	Pro	Thr	
		275						280					285				
45	Phe	His	Thr	Glu	Val	Ala	Glu	Pro	Phe	Lys	Pro	Asp	Arg	Glu	Asp	Gly	
		290					295					300					
50	Val	Leu	Ile	Ala	Pro	Pro	Pro	Pro	Pro	Pro	Pro	Pro	Pro	Pro	Pro	Pro	
	305					310					315					320	
55	Ala	Pro	Ala	Val	Leu	Val	Ser	Ala	Pro	Pro	Pro	Pro	Pro	Pro	Pro	Leu	
				325					330						335		
60	Ser	Thr	Ala	Ser	Pro	Gly	Gln	Gly	Thr	Arg	Glu	Asp	Glu	Ser	Arg	Gly	
				340				345						350			
65	Gly	Val	Arg	Pro	Ser	Ala	Pro	Val	Pro	Glu	Ala	Pro	Arg	Glu	Val	Val	
			355					360					365				
70	Glu	Pro	Ser	Ser	Gly	Arg	Ala	Thr	Leu	Leu	Glu	Ser	Ile	Arg	Gln	Ala	
		370					375					380					
75	Gly	Gly	Ile	Gly	Lys	Ala	Lys	Leu	Arg	Ser	Val	Lys	Glu	Arg	Lys	Leu	
	385					390					395					400	

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	Glu	Lys	Lys	Lys	Gln	Lys	Glu	Gln	Glu	Gln	Val	Arg	Ala	Thr	Gly	Gln	
					405					410					415		
5	Gly	Gly	Asp	Leu	Met	Ala	Asp	Leu	Phe	Asn	Lys	Leu	Val	Met	Arg	Arg	
				420					425					430			
10	Lys	Gly	Ile	Ser	Gly	Lys	Gly	Pro	Ala	Pro	Gly	Ala	Ser	Glu	Gly	Pro	
			435					440					445				
15	Gly	Gly	Ala	Phe	Ala	Arg	Met	Ser	Asp	Ser	Ile	Pro	Pro	Leu	Pro	Pro	
		450					455					460					
20	Pro	Gln	Gln	Pro	Pro	Gly	Glu	Glu	Asp	Glu	Asp	Asp	Trp	Glu	Ser		
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	Gln	Ser	Pro	Lys	Met	Ser	Val	Gln	Glu	Gln	Gly	Phe	Pro	Leu	Asp	Leu	
	1				5					10					15		
5	Gly	Ala	Ser	Phe	Thr	Glu	Asp	Ala	Pro	Arg	Pro	Pro	Val	Pro	Gly	Glu	
				20					25					30			
10	Glu	Gly	Glu	Leu	Val	Ser	Thr	Asp	Pro	Arg	Pro	Val	Ser	His	Ser	Phe	
			35					40					45				
15	Cys	Ser	Gly	Lys	Gly	Pro	Gly	Ile	Lys	Gly	Glu	Thr	Ser	Thr	Ala	Thr	
		50					55					60					
20	Pro	Arg	Arg	Ser	Asp	Leu	Asp	Leu	Gly	Tyr	Glu	Pro	Glu	Gly	Ser	Ala	
	65					70					75					80	
25	Ser	Pro	Thr	Pro	Pro	Tyr	Leu	Lys	Trp	Ala	Glu	Ser	Leu	His	Ser	Leu	
					85					90					95		
30	Leu	Asp	Asp	Gln	Asp	Gly	Ile	Asn	Leu	Phe	Arg	Thr	Phe	Leu	Lys	Gln	
				100					105					110			
35	Glu	Asp	Cys	Ala	Asp	Leu	Leu	Asp	Phe	Trp	Phe	Ala	Cys	Ser	Gly	Phe	
			115					120					125				
40	Arg	Lys	Leu	Glu	Pro	Cys	Asp	Ser	Asn	Glu	Glu	Lys	Arg	Leu	Lys	Leu	
		130					135					140					
45	Ala	Lys	Ala	Ile	Tyr	Arg	Lys	Tyr	Ile	Leu	Asp	Asn	Asn	Gly	Ile	Val	
	145					150					155					160	

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	Ser	Arg	Gln	Thr	Lys	Pro	Ala	Thr	Lys	Ser	Phe	Ile	Lys	Asp	Cys	Ile	165	170	175
5	Met	Lys	Gln	Leu	Ile	Asp	Pro	Ala	Met	Phe	Asp	Gln	Ala	Gln	Thr	Glu	180	185	190
10	Ile	Gln	Ser	Thr	Met	Glu	Glu	Asn	Thr	Tyr	Pro	Ser	Phe	Leu	Lys	Ser	195	200	205
	Asp	Ile	Tyr	Leu	Glu	Tyr	Thr	Arg	Thr	Gly	Ser	Glu	Ser	Pro	Lys	Leu	210	215	220
15	Cys	Ser	Asp	Gln	Ser	Ser	Gly	Ser	Gly	Thr	Gly	Lys	Gly	Ile	Pro	Gly	225	230	235
20	Tyr	Leu	Pro	Thr	Leu	Asn	Glu	Asp	Glu	Glu	Trp	Lys	Cys	Asp	Gln	Asp	245	250	255
25	Val	Asp	Glu	Asp	Asp	Gly	Arg	Asp	Pro	Gly	Pro	Pro	Gly	Arg	Leu	Thr	260	265	270
	Gln	Lys	Leu	Leu	Leu	Glu	Thr	Ala	Ala	Pro	Arg	Ala	Ser	Ala	Ser	Arg	275	280	285
30	Arg	Tyr	Ser	Glu	Gly	Arg	Glu	Phe	Arg	Tyr	Gly	Ser	Trp	Arg	Glu	Pro	290	295	300
35	Val	Asn	Pro	Tyr	Tyr	Val	Asn	Ser	Gly	Tyr	Ala	Leu	Ala	Pro	Ala	Thr	305	310	315
	Ser	Ala	Asn	Asp	Ser	Glu	Gln	Gln	Ser	Leu	Ser	Ser	Asp	Ala	Asp	Ser	325	330	335
40	Leu	Ser	Leu	Thr	Asp	Ser	Ser	Val	Asp	Gly	Val	Pro	Pro	Tyr	Arg	Ile	340	345	350
45	Arg	Lys	Gln	His	Arg	Arg	Glu	Met	Gln	Glu	Ser	Val	Gln	Val	Asn	Gly	355	360	365
50	Arg	Val	Pro	Leu	Pro	His	Ile	Pro	Arg	Thr	Tyr	Arg	Met	Pro	Lys	Glu	370	375	380
	Ile	Arg	Val	Glu	Pro	Gln	Lys	Phe	Ala	Ala	Glu	Leu	Ile	His	Arg	Leu	385	390	395
55	Glu	Ala	Ile	Gln	Arg	Thr	Arg	Glu	Ala	Glu	Glu	Lys	Leu	Glu	Glu	Arg	405	410	415

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	Leu	Lys	Arg	Val	Arg	Met	Glu	Glu	Glu	Gly	Glu	Asp	Gly	Asp	Val	Ser	
				420					425					430			
5	Cys	Gly	Pro	Pro	Gly	Ala	Ser	His	Lys	Leu	Pro	Ser	Ala	Pro	Ala	Trp	
			435					440					445				
10	His	His	Phe	Pro	Pro	Arg	Tyr	Ala	Asp	Met	Gly	Cys	Thr	Gly	Leu	Arg	
		450					455					460					
15	Asp	Ala	His	Glu	Glu	Asn	Pro	Glu	Ser	Ile	Leu	Asp	Glu	His	Val	Gln	
	465					470					475					480	
20	Arg	Val	Met	Arg	Thr	Pro	Gly	Cys	Gln	Ser	Pro	Gly	Pro	Gly	His	Arg	
					485					490					495		
25	Ser	Pro	Asp	Ser	Val	His	Val	Pro	Lys	Val	Pro	Gly	Val	Leu	Gly	Gly	
				500					505					510			
30	Ile	Ala	Pro	Gly	His	Gly	Lys	His	Ala	Leu	Lys	Ser	Gly	Ala	Lys	Leu	
			515					520					525				
35	Asp	Ala	Ala	Gly	Leu	His	Leu	His	Arg	His	Ser	His	His	His	Gly	His	
		530					535					540					
40	His	Gly	Leu	Ala	Arg	Pro	Lys	Glu	Gln	Ala	Glu	Ala	Glu	Ala	Ala	Arg	
	545					550					555					560	
45	Arg	Val	Gln	Ser	Ser	Phe	Ser	Trp	Ala	Leu	Glu	Gln	His	Gly	His	Thr	
					565					570					575		
50	Ala	Lys	Pro	Arg	Ser	His	Ser	Glu	Ser	Val	Gly	Ala	Ala	His	Ile	Thr	
				580					585					590			
55	Ser	Asp	Gly	Leu	Thr	Tyr	Ser	Gly	Lys	Ala	Gly	Thr	Thr	Cys	Lys	Arg	
		595						600					605				
60	Asn	Thr	Lys	Lys	Ala	Glu	Ser	Gly	Lys	Ser	Met	Gly	Ala	Glu	Ala	Pro	
		610					615					620					
65	Gly	Pro	Ser	Glu	Asp	Ala	Glu	Lys	Asn	Gln	Lys	Ile	Met	Gln	Trp	Ile	
	625					630					635					640	
70	Ile	Glu	Gly	Glu	Lys	Glu	Ile	Ser	Arg	His	Arg	Lys	Ala	Gly	His	Gly	
					645					650					655		
75	Ser	Ser	Gly	Thr	Lys	Lys	Gln	Gln	Gly	His	Glu	Ser	Ser	Arg	Pro	Leu	
				660					665					670			

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	Ser	Ile	Glu	Arg	Pro	Gly	Ala	Val	His	Pro	Trp	Val	Ser	Ala	Gln	Leu	
			675					680					685				
5	Arg	Asn	Ser	Val	Gln	Pro	Ser	His	Leu	Phe	Ile	Gln	Asp	Pro	Thr	Met	
		690					695					700					
10	Pro	Pro	Asn	Pro	Ala	Pro	Asn	Pro	Leu	Thr	Gln	Leu	Glu	Glu	Ala	Arg	
	705					710					715					720	
	Arg	Arg	Leu	Glu	Glu	Glu	Glu	Lys	Arg	Ala	Ser	Lys	Leu	Pro	Ser	Lys	
				725						730					735		
15	Gln	Arg	Met	Lys	Ser	Gln	Arg	Lys	Val	Gly	Ser	Ser	Ser	Thr	Gln	Pro	
			740						745					750			
20	Cys	Asp	Ser	Ile	Val	Val	Ala	Tyr	Tyr	Phe	Cys	Gly	Glu	Pro	Ile	Pro	
		755						760					765				
	Tyr	Arg	Thr	Leu	Val	Arg	Gly	Arg	Ala	Val	Thr	Leu	Gly	Gln	Phe	Lys	
25		770					775					780					
	Glu	Leu	Leu	Thr	Lys	Lys	Gly	Asn	Tyr	Arg	Tyr	Tyr	Phe	Lys	Lys	Val	
	785					790					795					800	
30	Ser	Asp	Glu	Phe	Asp	Cys	Gly	Val	Val	Phe	Glu	Glu	Val	Arg	Glu	Asp	
					805					810					815		
35	Glu	Ala	Val	Leu	Pro	Val	Phe	Glu	Glu	Lys	Ile	Ile	Gly	Lys	Val	Glu	
				820					825					830			
40	Lys	Val	Asp														
			835														

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45 <213> Equus caballus

<400> 25

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Val Ala Gly Val Arg Pro Pro Ile Met Asn Gly Pro Met His Pro Arg
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5 Pro Leu Val Ala Leu Leu Asp Gly Arg Asp Cys Thr Val Glu Met Pro
20 25 30

10 Ile Leu Lys Asp Val Ala Thr Val Ala Phe Cys Asp Ala Gln Ser Thr
35 40 45

Gln Glu Ile His Glu Lys Val Leu Asn Glu Ala Val Gly Ala Leu Met
50 55 60

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	Tyr	His	Thr	Ile	Thr	Leu	Thr	Arg	Glu	Asp	Leu	Glu	Lys	Phe	Lys	Ala	
	65					70					75					80	
5	Leu	Arg	Ile	Ile	Val	Arg	Ile	Gly	Ser	Gly	Phe	Asp	Asn	Ile	Asp	Ile	
					85					90					95		
10	Lys	Ser	Ala	Gly	Asp	Leu	Gly	Ile	Ala	Val	Cys	Asn	Val	Pro	Ala	Ala	
				100					105					110			
15	Ser	Val	Glu	Glu	Thr	Ala	Asp	Ser	Thr	Met	Cys	His	Ile	Leu	Asn	Leu	
			115					120					125				
20	Tyr	Arg	Arg	Thr	Thr	Trp	Leu	His	Gln	Ala	Leu	Arg	Glu	Gly	Thr	Arg	
		130					135					140					
25	Val	Gln	Ser	Val	Glu	Gln	Ile	Arg	Glu	Val	Ala	Ser	Gly	Ala	Ala	Arg	
	145					150					155					160	
30	Ile	Arg	Gly	Glu	Thr	Leu	Gly	Ile	Ile	Gly	Leu	Gly	Arg	Val	Gly	Gln	
					165					170					175		
35	Ala	Val	Ala	Leu	Arg	Ala	Lys	Ala	Phe	Gly	Phe	Asn	Val	Leu	Phe	Tyr	
				180					185					190			
40	Asp	Pro	Tyr	Leu	Ser	Asp	Gly	Thr	Glu	Arg	Ala	Leu	Gly	Leu	Gln	Arg	
			195					200					205				
45	Val	Ser	Thr	Leu	Gln	Asp	Leu	Leu	Phe	His	Ser	Asp	Cys	Val	Thr	Leu	
		210					215					220					
50	His	Cys	Gly	Leu	Asn	Glu	His	Asn	His	His	Leu	Ile	Asn	Asp	Phe	Thr	
	225					230					235					240	
55	Val	Lys	Gln	Met	Arg	Gln	Gly	Ala	Phe	Leu	Val	Asn	Thr	Ala	Arg	Gly	
					245					250					255		
60	Gly	Leu	Val	Asp	Glu	Lys	Ala	Leu	Ala	Gln	Ala	Leu	Lys	Glu	Gly	Arg	
				260					265					270			
65	Ile	Arg	Gly	Ala	Ala	Leu	Asp	Val	His	Glu	Ser	Glu	Pro	Phe	Ser	Phe	
			275					280					285				
70	Ser	Gln	Gly	Pro	Leu	Lys	Asp	Ala	Pro	Asn	Leu	Ile	Cys	Thr	Pro	His	
		290					295					300					
75	Ala	Ala	Trp	Tyr	Ser	Glu	Gln	Ala	Ser	Ile	Glu	Met	Arg	Glu	Glu	Ala	
	305					310					315					320	

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	Ala	Arg	Glu	Ile	Arg	Arg	Ala	Ile	Thr	Gly	Arg	Ile	Pro	Asp	Ser	Leu
					325					330					335	
5	Lys	Asn	Cys	Val	Asn	Lys	Asp	His	Leu	Thr	Ala	Ala	Thr	His	Trp	Ala
				340					345					350		
10	Ser	Met	Asp	Pro	Ala	Val	Val	His	Pro	Glu	Leu	Asn	Gly	Ala	Ala	Tyr
			355					360					365			
15	Arg	Tyr	Pro	Pro	Gly	Val	Val	Gly	Val	Ala	Pro	Ser	Gly	Ile	Pro	Ala
		370					375					380				
20	Ala	Val	Glu	Gly	Ile	Val	Pro	Ser	Ala	Met	Ser	Leu	Ser	His	Gly	Leu
	385					390					395					400
25	Pro	Pro	Val	Ser	His	Pro	Pro	His	Ala	Pro	Ser	Pro	Gly	Gln	Thr	Val
					405					410					415	
30	Lys	Pro	Glu	Ala	Asp	Arg	Asp	His	Pro	Ser	Asp	Gln	Leu			
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	Met	Asp	Lys	Phe	Trp	Trp	Arg	Ala	Ala	Trp	Gly	Leu	Cys	Leu	Val	Pro	
	1				5					10					15		
5	Leu	Ser	Leu	Ala	Gln	Ile	Asp	Leu	Asn	Ile	Thr	Cys	Arg	Tyr	Ala	Gly	
				20					25					30			
	Val	Phe	His	Val	Glu	Lys	Asn	Gly	Arg	Tyr	Ser	Ile	Ser	Arg	Thr	Glu	
10			35					40					45				
	Ala	Ala	Asp	Leu	Cys	Lys	Ala	Phe	Asn	Ser	Thr	Leu	Pro	Thr	Met	Ala	
		50					55					60					
15	Gln	Met	Gln	Lys	Ala	Leu	Asn	Ile	Gly	Phe	Glu	Thr	Cys	Arg	Tyr	Gly	
	65					70					75					80	
	Phe	Ile	Glu	Gly	His	Val	Val	Ile	Pro	Arg	Ile	His	Pro	Asn	Ser	Ile	
20					85					90					95		
	Cys	Ala	Ala	Asn	Asn	Thr	Gly	Val	Tyr	Ile	Leu	Thr	Ser	Asn	Thr	Ser	
25				100					105					110			
	Gln	Tyr	Asp	Thr	Tyr	Cys	Phe	Asn	Ala	Ser	Ala	Pro	Pro	Glu	Glu	Asp	
30																	
35																	
40																	
45																	
50																	
55																	

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	115					120					125					
5	Cys	Thr	Ser	Val	Thr	Asp	Leu	Pro	Asn	Ala	Phe	Glu	Gly	Pro	Ile	Thr
	130						135					140				
	Ile	Thr	Ile	Val	Asn	Arg	Asp	Gly	Thr	Arg	Tyr	Thr	Lys	Lys	Gly	Glu
	145					150					155					160
10	Tyr	Arg	Thr	Asn	Pro	Glu	Asp	Ile	Asn	Pro	Ser	Thr	Pro	Ala	Asp	Asp
					165					170					175	
15	Asp	Val	Ser	Ser	Gly	Ser	Ser	Ser	Glu	Arg	Ser	Thr	Ser	Gly	Gly	Tyr
				180					185					190		
	Ser	Ile	Phe	His	Thr	His	Leu	Pro	Thr	Thr	Arg	Pro	Thr	Gln	Asp	Gln
			195					200					205			
20	Ser	Ser	Pro	Trp	Val	Ser	Asp	Ser	Pro	Glu	Lys	Thr	Pro	Thr	Thr	Ser
	210						215					220				
25	Thr	Asp	Ser	Asn	Val	Ile	Ser	Ala	Gly	Trp	Glu	Pro	Pro	Glu	Glu	Asn
	225					230					235					240
	Glu	Asp	Glu	Arg	Asp	Lys	His	Pro	Ser	Tyr	Ser	Gly	Ser	Gly	Ile	Asp
					245					250					255	
30	Asp	Asp	Glu	Asp	Phe	Val	Ser	Ser	Thr	Ile	Pro	Thr	Lys	Pro	Arg	Ile
				260					265					270		
35	Phe	Lys	Phe	Pro	Glu	Val	Asn	Glu	Asp	Trp	Arg	Gln	Trp	Ser	Pro	Gly
			275					280					285			
	His	Ser	Thr	Pro	Gly	Ile	Leu	Leu	Gln	Thr	Ala	Thr	Arg	Met	Thr	Asp
40		290					295					300				
	Val	Asp	Arg	Ser	Gly	Thr	Ser	Ala	Tyr	Gly	Glu	Ser	Gln	Thr	Gln	Glu
	305					310					315					320
45	Pro	His	Ser	Pro	Leu	Val	His	His	Glu	His	His	Asp	Glu	Glu	Glu	Thr
					325					330					335	
	Gln	His	Ser	Thr	Ser	Ser	Thr	Trp	Ala	Leu	Ser	Ser	Arg	Thr	Ala	Glu
50				340					345					350		
	Asp	Thr	Ala	Thr	Gln	Lys	Glu	Gln	Trp	Phe	Glu	Asp	Gly	Trp	Arg	Gly
			355					360					365			
55	Glu	Tyr	Thr	Gln	Thr	Pro	Lys	Glu	Asp	Ser	Pro	Ser	Ala	Thr	Gly	Thr
	370						375					380				

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	Ala	Val	Thr	Thr	Ala	Ser	Ala	His	Asp	Ser	His	Pro	Asn	Arg	Arg	Met	
	385					390					395					400	
5	Thr	Thr	Gln	Ser	Gln	Glu	Asp	Ser	Ser	Trp	Thr	Tyr	Phe	Phe	Asp	Pro	
					405					410					415		
10	Ile	Ser	His	Pro	Lys	Gly	Arg	Gly	His	His	Thr	Glu	Arg	Trp	Met	Asp	
				420					425					430			
15	Val	Asp	Ser	Ser	Arg	Ser	Thr	Thr	Leu	Gln	Pro	Ser	Ala	Asp	Pro	Ser	
			435					440					445				
20	Thr	Gly	Leu	Val	Glu	Glu	Leu	Asp	Arg	Thr	Arg	Pro	Leu	Ser	Met	Thr	
		450					455					460					
25	Thr	Gln	Gln	Ser	His	Thr	Gln	Ser	Phe	Ser	Thr	Ser	His	Gly	Gly	Leu	
	465					470					475					480	
30	Glu	Glu	Asp	Lys	Asp	His	Pro	Met	Thr	Ser	Thr	Pro	Ser	Ser	Ser	Asn	
				485						490					495		
35	Arg	Asn	Asp	Gly	Arg	Gly	Gly	Arg	Arg	Ser	Gly	Asn	Phe	Ser	Glu	Asp	
				500				505						510			
40	Ser	Ala	Thr	Ser	Gly	Glu	Gly	Tyr	Thr	Ala	His	Ala	Pro	Asp	Thr	Lys	
			515					520					525				
45	Glu	Tyr	Asn	Thr	Leu	Thr	Pro	Val	Thr	Pro	Ala	Lys	Thr	Gly	Ser	Pro	
		530					535					540					
50	Gly	Val	Thr	Glu	Val	Ile	Val	Leu	Asp	Asp	Ser	Asn	Ser	His	Val	Asp	
	545					550					555					560	
55	Gly	Ser	Phe	Ser	Gly	Asn	Leu	Ala	Thr	Tyr	Arg	Ala	Ser	Gly	Gly	Arg	
					565					570					575		
60	Ala	Gln	Thr	Thr	His	Gly	Ser	Glu	Thr	Ser	Gly	His	Ser	Thr	Gly	Ser	
				580					585					590			
65	Gln	Glu	Gly	Gly	Ala	Ser	Thr	Thr	Ser	Gly	Pro	Ile	Arg	Arg	Pro	Gln	
			595					600					605				
70	Ile	Pro	Glu	Trp	Leu	Ile	Ile	Leu	Ala	Ser	Leu	Leu	Ala	Leu	Ala	Leu	
		610					615					620					
75	Ile	Leu	Ala	Val	Cys	Ile	Ala	Val	Asn	Ser	Arg	Arg	Arg	Cys	Gly	Gln	
	625					630					635					640	

Lys Lys Lys Leu Val Ile Asn Asn Gly Asn Gly Ala Val Asp Asp Arg
645 650 655

Lys Ala Ser Gly Leu Asn Gly Glu Ala Ser Arg Ser Gln Glu Met Val
660 665 670

His Leu Val Asn Lys Glu Ser Ser Glu Thr Gln Asp Gln Phe Met Thr
675 680 685

Ala Asp Glu Thr Arg Asn Leu Gln Asn Val Asp Met Lys Ile Gly Val
690 695 700

Claims

1. An *in vitro* method or assay for the diagnosis of osteochondrosis or prediction of the likelihood of its onset in a horse which is not more than 12 months old, comprising the steps
 - a) measuring the expression level of a marker in a sample obtained from said horse with an agent that can be used to determine the expression level of said marker, and
 - b) comparing the expression level measured in step a) to the expression level of said marker measured in a sample obtained from one or more horses not affected by osteochondrosis,

characterized in that the marker is ApoB-3G,
wherein an increase in the expression level of ApoB-3G is indicative of osteochondrosis.
2. The *in vitro* method or assay according to claim 1, **characterized in that** the expression levels of one or more additional markers are measured,
wherein the additional markers are selected from the list consisting of
Dsh1, wherein a decrease in the expression level of Dsh1 is indicative of osteochondrosis;
Foxl1, wherein a decrease in the expression level of Foxl1 is indicative of osteochondrosis;
Hp, wherein a decrease in the expression level of Hp is indicative of osteochondrosis;
ISG17, wherein a decrease in the expression level of ISG17 is indicative of osteochondrosis;
Mark2, wherein a decrease in the expression level of Mark2 is indicative of osteochondrosis;
PPP2R1A-a, wherein an increase or decrease in the expression level of PPP2R1A-a is indicative of osteochondrosis;
PPP2R1A-b, wherein an increase or decrease in the expression level of PPP2R1A-b is indicative of osteochondrosis;
RUSC2, wherein a decrease in the expression level of RUSC2 is indicative of osteochondrosis; and
WASH1, wherein an increase or decrease in the expression level of WASH1 is indicative of osteochondrosis.
3. The *in vitro* method or assay according to claim 2, **characterized in that** the expression levels of the additional markers Dsh1, Foxl1, Hp, PPP2R1A-a, RUSC2 and WASH1 are measured.
4. The *in vitro* method or assay according to claim 2, **characterized in that** the expression levels of all of the additional markers are measured.
5. The *in vitro* method or assay according to claim 1, **characterized in that** the expression levels of at least one, two, several or all of the additional markers Dsh1, Foxl1, Hp, PPP2R1A-a, RUSC2 and WASH1 are measured, wherein the expression levels of Dsh1, Foxl1, Hp, PPP2R1A-a, RUSC2 and WASH1 are further used to diagnose and/or predict whether the fetlock joint, the hock joint or the stifle joint is or will be affected by osteochondrosis.
6. The *in vitro* method or assay according to claim 1 or 5, **characterized in that** the expression levels of at least one, two, several or all of the additional markers Dsh1, Foxl1, Hp, PPP2R1A-a, RUSC2 and WASH1 are measured, wherein
an increase in the expression level of each PPP2R1A-a and WASH1, a decrease in the expression level of each Dsh1, Foxl1, Hp and RUSC2 is indicative of affection of the fetlock joint;
a decrease in the expression level of each Dsh1, Hp, PPP2R1A-a, RUSC2 and WASH1 and no change in the

expression level of Foxl1 is indicative of affection of the hock joint; and
a decrease in the expression level of each Dsh1, Foxl1, Hp, PPP2R1A-a, RUSC2 and WASH1 is indicative of affection of the stifle joint.

- 5 7. The *in vitro* method or assay according to claim 5 or 6, **characterized in that** the expression levels of at least the markers of one of the following marker combinations are measured: Foxl1-and WASH1; or Foxl1 and PPP2R1A-a.
8. The *in vitro* method or assay according to claim 1, **characterized in that** the expression levels of at least one, two, several or all of the additional markers Dsh1, Foxl1, Hp, Mark2, PPP2R1A-a, WASH1, ISG17, PPP2R1A-b and RUSC2 are measured, wherein the expression levels of Dsh1, Foxl1, Hp, Mark2, PPP2R1A-a, WASH1, ISG17, PPP2R1A-b and RUSC2 are further used to diagnose and/or predict whether the fetlock joint, the hock joint or the stifle joint is or will be affected by osteochondrosis.
- 10 9. The *in vitro* method or assay according to claim 1 or 8, **characterized in that** the expression levels of at least one, two, several or all of the additional markers Dsh1, Foxl1, Hp, Mark2, PPP2R1A-a, WASH1, ISG17, PPP2R1A-b and RUSC2 are measured, wherein
15 an increase in the expression level of each PPP2R1A-a, PPP2R1A-b and WASH1, a decrease in the expression level of each Dsh1, Foxl1, Hp, Mark2 and RUSC2 and no change in the expression level of ISG17 is indicative of affection of the fetlock joint;
20 a decrease in the expression level of each Dsh1, Hp, ISG17, Mark2, PPP2R1A-a, PPP2R1A-b, RUSC2 and WASH1 and no change in the expression level of Foxl1 is indicative of affection of the hock joint; and
a decrease in the expression level of each Dsh1, Foxl1, Hp, ISG17, Mark2, PPP2R1A-a, PPP2R1A-b, RUSC2 and WASH1 is indicative of affection of the stifle joint.
- 25 10. The *in vitro* method or assay according to claim 8 or 9, **characterized in that** the expression levels of at least the markers of one of the following marker combinations are measured: Foxl1 and WASH1; or Foxl1 and PPP2R1A-a; or Foxl1 and PPP2R1A-b.
11. The *in vitro* method according to any one of claims 1 to 10 **characterized in that** the expression levels of the markers are determined by measuring the mRNA of the corresponding marker.
- 30 12. The *in vitro* method according to any one of claims 1 to 11 **characterized in that** the samples are blood samples.
13. Use of a kit in a method for the diagnosis of osteochondrosis or prediction of the likelihood of its onset in a horse which is not more than 12 months old, wherein the expression level of a marker in a sample obtained from said horse is measured, and
35 said expression level is compared to the expression level of said marker measured in a sample obtained from one or more horses not affected by osteochondrosis,
wherein the kit comprises at least one agent, which binds specifically to the product of the gene of the respective marker and which can be used to determine the expression level of said marker, wherein the marker is ApoB-3G;
40 wherein the kit optionally comprises additional agent(s) for measuring the expression level of one or more additional markers and/or for measuring the expression levels of one or more housekeeping genes.
14. The use according to claim 13, wherein the kit further comprises
45 a) additional agent(s) each for measuring the expression level of a marker selected from the list consisting of Dsh1, Foxl1, Hp, ISG17, Mark2, PPP2R1A-a, PPP2R1A-b, RUSC2 and WASH1, wherein each additional agent binds specifically to the product of the gene of the respective marker and which can be used to determine the expression level of the respective marker; and/or
50 b) additional agent(s) for measuring the expression level of a housekeeping gene selected from the list consisting of Axin1, CtBP1 and CD44, wherein each additional agent binds specifically to the gene product of the respective housekeeping gene and can be used to determine the expression level of the respective housekeeping gene.
15. The use according to claim 13 or 14, wherein each agent is an oligonucleotide primer set comprising
55 a forward primer with a length of 10 to 40 nucleotides that possesses at least 70% sequence identity with a continuous sequence of the same length selected from the DNA sequence of the respective marker or housekeeping gene (SEQ ID NO: 1 to 13), and
either a reverse primer with a length of 10 to 40 nucleotides that possesses at least 70% sequence identity with a

continuous sequence of the same length selected from the sequence complementary to the DNA sequence of the respective marker or housekeeping gene (SEQ ID NO: 1 to 13), or
 a reverse primer with a length of 10 to 40 nucleotides that possesses at least 70% sequence identity with a continuous polyadenosine or polythymidine sequence of the same length.

Patentansprüche

1. In-vitro-Verfahren oder -Assay für die Diagnose von Osteochondrose oder Vorhersage der Wahrscheinlichkeit ihres Beginns bei einem Pferd, das nicht älter als 12 Monate ist, umfassend die folgenden Schritte:

a) Messen des Expressionsniveaus eines Markers in einer von dem Pferd entnommenen Probe mit einem Agens, mit dem das Expressionsniveau des Markers bestimmt werden kann, und
 b) Vergleichen des in Schritt a) gemessenen Expressionsniveaus mit dem Expressionsniveau des Markers, das in einer Probe gemessen wurde, die von einem oder mehreren Pferden, die nicht an Osteochondrose leiden, entnommen wurde,
dadurch gekennzeichnet, dass
 es sich bei dem Marker um ApoB-3G handelt,
 wobei ein Ansteigen des Expressionsniveaus von ApoB-3G Osteochondrose anzeigt.

2. In-vitro-Verfahren oder -Assay nach Anspruch 1, **dadurch gekennzeichnet, dass** die Expressionsniveaus von einem oder mehreren zusätzlichen Markern gemessen werden, wobei die zusätzlichen Marker aus der Liste bestehend aus den Folgenden ausgewählt sind:

Dsh1, wobei eine Verringerung des Expressionsniveaus von Dsh1 Osteochondrose anzeigt;
 Foxl1, wobei eine Verringerung des Expressionsniveaus von Foxl1 Osteochondrose anzeigt;
 Hp, wobei eine Verringerung des Expressionsniveaus von Hp Osteochondrose anzeigt;
 ISG17, wobei eine Verringerung des Expressionsniveaus von ISG17 Osteochondrose anzeigt;
 Mark2, wobei eine Verringerung des Expressionsniveaus von Mark2 Osteochondrose anzeigt;
 PPP2R1A-a, wobei ein Ansteigen oder eine Verringerung des Expressionsniveaus von PPP2R1A-a Osteochondrose anzeigt;
 PPP2R1A-b, wobei ein Ansteigen oder eine Verringerung des Expressionsniveaus von PPP2R1A-b Osteochondrose anzeigt;
 RUSC2, wobei eine Verringerung des Expressionsniveaus von RUSC2 Osteochondrose anzeigt; und
 WASH1, wobei ein Ansteigen oder eine Verringerung des Expressionsniveaus von WASH1 Osteochondrose anzeigt.

3. In-vitro-Verfahren oder -Assay nach Anspruch 2, **dadurch gekennzeichnet, dass** die Expressionsniveaus der zusätzlichen Marker Dsh1, Foxl1, Hp, PPP2R1A-a, RUSC2 und WASH1 gemessen werden.

4. In-vitro-Verfahren oder -Assay nach Anspruch 2, **dadurch gekennzeichnet, dass** die Expressionsniveaus von allen der zusätzlichen Marker gemessen werden.

5. In-vitro-Verfahren oder -Assay nach Anspruch 1, **dadurch gekennzeichnet, dass** die Expressionsniveaus von mindestens einem, zwei, mehreren oder allen der zusätzlichen Marker Dsh1, Foxl1, Hp, PPP2R1A-a, RUSC2 und WASH1 gemessen werden, wobei die Expressionsniveaus von Dsh1, Foxl1, Hp, PPP2R1A-a, RUSC2 und WASH1 weiterhin dazu verwendet werden, um zu diagnostizieren und/oder vorherzusagen, ob das Fesselgelenk, das Sprunggelenk oder das Kniegelenk an Osteochondrose leidet oder daran leiden wird.

6. In-vitro-Verfahren oder -Assay nach Anspruch 1 oder 5, **dadurch gekennzeichnet, dass** die Expressionsniveaus von mindestens einem, zwei, mehreren oder allen der zusätzlichen Marker Dsh1, Foxl1, Hp, PPP2R1A-a, RUSC2 und WASH1 gemessen werden, wobei
 ein Ansteigen ein des Expressionsniveaus von jeweils PPP2R1A-a und WASH1, eine Verringerung des Expressionsniveaus von jeweils Dsh1, Foxl1, Hp und RUSC2 anzeigen, dass ein Leiden des Fesselgelenks besteht;
 eine Verringerung des Expressionsniveaus von jeweils Dsh1, Hp, PPP2R1A-a, RUSC2 und WASH1 und keine Veränderung des Expressionsniveaus von Foxl1 anzeigen, dass ein Leiden des Sprunggelenks besteht; und
 eine Verringerung des Expressionsniveaus von jeweils Dsh1, Foxl1, Hp, PPP2R1A-a, RUSC2 und WASH1 anzeigt, dass ein Leiden des Kniegelenks besteht.

7. In-vitro-Verfahren oder -Assay nach Anspruch 5 oder 6, **dadurch gekennzeichnet, dass** die Expressionsniveaus von mindestens der Marker von einer der folgenden Markerkombinationen gemessen werden: Foxl1 und WASH1; oder Foxl1 und PPP2R1A-a.

8. In-vitro-Verfahren oder -Assay nach Anspruch 1, **dadurch gekennzeichnet, dass** die Expressionsniveaus von mindestens einem, zwei, mehreren oder allen der zusätzlichen Marker Dsh1, Foxl1, Hp, Mark2, PPP2R1A-a, WASH1, ISG17, PPP2R1A-b und RUSC2 gemessen werden, wobei die Expressionsniveaus von Dsh1, Foxl1, Hp, Mark2, PPP2R1A-a, WASH1, ISG17, PPP2R1A-b und RUSC2 weiterhin dazu verwendet werden, um zu diagnostizieren und/oder vorherzusagen, ob das Fesselgelenk, das Sprunggelenk oder das Kniegelenk an Osteochondrose leidet oder daran leiden wird.

9. In-vitro-Verfahren oder -Assay nach Anspruch 1 oder 8, **dadurch gekennzeichnet, dass** die Expressionsniveaus von mindestens einem, zwei, mehreren oder allen der zusätzlichen Marker Dsh1, Foxl1, Hp, Mark2, PPP2R1A-a, WASH1, ISG17, PPP2R1A-b und RUSC2 gemessen werden, wobei ein Ansteigen des Expressionsniveaus von jeweils PPP2R1A-a, PPP2R1A-b und WASH1, eine Verringerung des Expressionsniveaus von jeweils Dsh1, Foxl1, Hp, Mark2 und RUSC2 und keine Veränderung des Expressionsniveaus von ISG17 anzeigen, dass ein Leiden des Fesselgelenks besteht; eine Verringerung des Expressionsniveaus von jeweils Dsh1, Hp, ISG17, Mark2, PPP2R1A-a, PPP2R1A-b, RUSC2 und WASH1 und keine Veränderung des Expressionsniveaus von Foxl1 anzeigen, dass ein Leiden des Sprunggelenks besteht; und eine Verringerung des Expressionsniveaus von jeweils Dsh1, Foxl1, Hp, ISG17, Mark2, PPP2R1A-a, PPP2R1A-b, RUSC2 und WASH1 anzeigt, dass ein Leiden des Kniegelenks besteht.

10. In-vitro-Verfahren oder -Assay nach Anspruch 8 oder 9, **dadurch gekennzeichnet, dass** die Expressionsniveaus von mindestens den Markern von einer der folgenden Markerkombinationen gemessen werden: Foxl1 und WASH1; oder Foxl1 und PPP2R1A-a; oder Foxl1 und PPP2R1A-b.

11. In-vitro-Verfahren nach einem der Ansprüche 1 bis 10, **dadurch gekennzeichnet, dass** die Expressionsniveaus der Marker durch Messen der mRNA des entsprechenden Markers bestimmt werden.

12. In-vitro-Verfahren nach einem der Ansprüche 1 bis 11, **dadurch gekennzeichnet, dass** es sich bei den Proben um Blutproben handelt.

13. Verwendung eines Kits in einem Verfahren für die Diagnose von Osteochondrose oder Vorhersage der Wahrscheinlichkeit ihres Beginns bei einem Pferd, das nicht älter als 12 Monate ist, wobei das Expressionsniveau eines Markers in einer Probe, die von dem Pferd entnommen wurde, gemessen wird, und das Expressionsniveau mit dem Expressionsniveau des Markers, das in einer Probe, die von einem oder mehreren Pferden, die nicht an Osteochondrose leiden, entnommen wurde, gemessen wurde, verglichen wird, wobei das Kit mindestens ein Agens, das spezifisch an das Produkt des Gens des entsprechenden Markers bindet und mit dem das Expressionsniveau des Markers bestimmt werden kann, umfasst, wobei es sich bei dem Marker um ApoB-3G handelt; wobei das Kit gegebenenfalls ein zusätzliches Agens bzw. zusätzliche Agenzien zum Messen des Expressionsniveaus von einem oder mehreren zusätzlichen Markern und/oder zum Messen der Expressionsniveaus von einem oder mehreren "Housekeeping"-Genen umfasst.

14. Verwendung nach Anspruch 13, wobei das Kit weiterhin Folgendes umfasst:

a) ein zusätzliches Agens bzw. zusätzliche Agenzien, mit dem bzw. mit denen jeweils das Expressionsniveau eines Markers, ausgewählt aus der Liste bestehend aus Dsh1, Foxl1, Hp, ISG17, Mark2, PPP2R1A-a, PPP2R1A-b, RUSC2 und WASH1, gemessen werden kann, wobei jedes zusätzliche Agens spezifisch an das Produkt des Gens des jeweiligen Markers bindet und mit dem das Expressionsniveau des jeweiligen Markers bestimmt werden kann; und/oder

b) ein zusätzliches Agens bzw. zusätzliche Agenzien zum Messen des Expressionsniveaus eines "Housekeeping"-Gens, ausgewählt aus der Liste bestehend aus Axin1, CtBP1 und CD44, wobei jedes zusätzliche Agens spezifisch an das Genprodukt des jeweiligen "Housekeeping"-Gens bindet und mit dem das Expressionsniveau des jeweiligen "Housekeeping"-Gens bestimmt werden kann.

15. Verwendung nach Anspruch 13 oder 14, wobei es sich bei jedem Agens um einen Oligonukleotid-Primer-Satz

handelt, der Folgendes umfasst:

einen Forward-Primer mit einer Länge von 10 bis 40 Nukleotiden, der mindestens 70% Sequenzidentität zu einer kontinuierlichen Sequenz derselben Länge, ausgewählt aus der DNA-Sequenz des jeweiligen Markers oder "Housekeeping"-Gens (SEQ ID NO: 1 bis 13), aufweist, und
entweder einen Reverse-Primer mit einer Länge von 10 bis 40 Nukleotiden, der mindestens 70% Sequenzidentität zu einer kontinuierlichen Sequenz derselben Länge, ausgewählt aus der Sequenz, die zu der DNA-Sequenz des jeweiligen Markers oder "Housekeeping"-Gens (SEQ ID NO: 1 bis 13) komplementär ist, aufweist, oder einen Reverse-Primer mit einer Länge von 10 bis 40 Nukleotiden, der mindestens 70% Sequenzidentität zu einer kontinuierlichen Polyadenosin- oder Polythymidin-Sequenz derselben Länge aufweist.

Revendications

1. Procédé ou essai *in vitro* pour le diagnostic de l'ostéochondrose ou la prédiction de la probabilité de son apparition chez un cheval qui n'est pas âgé de plus de 12 mois, comprenant les étapes de
 - a) mesure du taux d'expression d'un marqueur dans un échantillon obtenu à partir dudit cheval avec un agent qui peut être utilisé pour déterminer le taux d'expression dudit marqueur, et
 - b) comparaison du taux d'expression mesuré dans l'étape a) au taux d'expression dudit marqueur mesuré dans un échantillon obtenu à partir d'un ou plusieurs chevaux non affectés par l'ostéochondrose, **caractérisé en ce que** le marqueur est ApoB-3G, où une augmentation du taux d'expression de ApoB-3G est indicative de l'ostéochondrose.
2. Procédé ou essai *in vitro* selon la revendication 1, **caractérisé en ce que** les taux d'expression d'un ou plusieurs marqueurs additionnels sont mesurés, où les marqueurs additionnels sont choisis dans la liste constituée de Dsh1, où une diminution du taux d'expression de Dsh1 est indicative de l'ostéochondrose ;
Foxl1, où une diminution du taux d'expression de Foxl1 est indicative de l'ostéochondrose ;
Hp, où une diminution du taux d'expression de Hp est indicative de l'ostéochondrose ;
ISG17, où une diminution du taux d'expression de ISG17 est indicative de l'ostéochondrose ;
Mark2, où une diminution du taux d'expression de Mark2 est indicative de l'ostéochondrose ;
PPP2R1A-a, où une augmentation ou diminution du taux d'expression de PPP2R1A-a est indicative de l'ostéochondrose ;
PPP2R1 A-b, où une augmentation ou diminution du taux d'expression de PPP2R1A-b est indicative de l'ostéochondrose ;
RUSC2, où une diminution du taux d'expression de RUSC2 est indicative de l'ostéochondrose ; et
WASH1, où une augmentation ou diminution du taux d'expression de WASH1 est indicative de l'ostéochondrose.
3. Procédé ou essai *in vitro* selon la revendication 2, **caractérisé en ce que** les taux d'expression des marqueurs additionnels Dsh1, Foxl1, Hp, PPP2R1A-a, RUSC2 et WASH1 sont mesurés.
4. Procédé ou essai *in vitro* selon la revendication 2, **caractérisé en ce que** les taux d'expression de tous les marqueurs additionnels sont mesurés.
5. Procédé ou essai *in vitro* selon la revendication 1, **caractérisé en ce que** les taux d'expression d'au moins un, deux, plusieurs ou tous les marqueurs additionnels Dsh1, Foxl1, Hp, PPP2R1A-a, RUSC2 et WASH1 sont mesurés, où les taux d'expression de Dsh1, Foxl1, Hp, PPP2R1A-a, RUSC2 et WASH1 sont en outre utilisés pour diagnostiquer et/ou prédire si l'articulation du boulet, l'articulation du jarret ou l'articulation du grasset est ou sera affectée par l'ostéochondrose.
6. Procédé ou essai *in vitro* selon la revendication 1 ou 5, **caractérisé en ce que** les taux d'expression d'au moins un, deux, plusieurs ou tous les marqueurs additionnels Dsh1, Foxl1, Hp, PPP2R1A-a, RUSC2 et WASH1 sont mesurés, où
une augmentation du taux d'expression de chacun de PPP2R1A-a et WASH1, une diminution du taux d'expression de chacun de Dsh1, Foxl1, Hp et RUSC2 est indicative d'une affection de l'articulation du boulet ;
une diminution du taux d'expression de chacun de Dsh1, Hp, PPP2R1A-a, RUSC2 et WASH1 et aucun changement du taux d'expression de Foxl1 est indicatif d'une affection de l'articulation du jarret ; et
une diminution du taux d'expression de chacun de Dsh1, Foxl1, Hp, PPP2R1A-a, RUSC2 et WASH1 est indicative

de l'affection de l'articulation du grasset.

7. Procédé ou essai *in vitro* selon la revendication 5 ou 6, **caractérisé en ce que** les taux d'expression d'au moins les marqueurs d'une des combinaisons de marqueurs suivantes sont mesurés : Foxl1 et WASH1 ; ou Foxl1 et PPP2R1A-a.
8. Procédé ou essai *in vitro* selon la revendication 1, **caractérisé en ce que** les taux d'expression d'au moins un, deux, plusieurs ou tous les marqueurs additionnels Dsh1, Foxl1, Hp, Mark2, PPP2R1A-a, WASH1, ISG17, PPP2R1A-b et RUSC2 sont mesurés, où les taux d'expression de Dsh1, Foxl1, Hp, Mark2, PPP2R1A-a, WASH1, ISG17, PPP2R1A-b et RUSC2 sont en outre utilisés pour diagnostiquer et/ou prédire si l'articulation du boulet, l'articulation du jarret ou l'articulation du grasset est ou sera affecté par l'ostéochondrose.
9. Procédé ou essai *in vitro* selon la revendication 1 ou 8, **caractérisé en ce que** les taux d'expression d'au moins un, deux, plusieurs ou tous les marqueurs additionnels Dsh1, Foxl1, Hp, Mark2, PPP2R1A-a, WASH1, ISG17, PPP2R1A-b et RUSC2 sont mesurés, où une augmentation du taux d'expression de chacun de PPP2R1A-a, PPP2R1A-b et WASH1, une diminution du taux d'expression de chacun de Dsh1, Foxl1, Hp, Mark2 et RUSC2 et aucun changement du taux d'expression de ISG17 est indicatif d'une affection de l'articulation du boulet ; une diminution du taux d'expression de chacun de Dsh1, Hp, ISG17, Mark2, PPP2R1A-a, PPP2R1A-b, RUSC2 et WASH1 et aucun changement du taux d'expression de Foxl1 est indicatif d'une affection de l'articulation du jarret ; et une diminution du taux d'expression de chacun de Dsh1, Foxl1, Hp, ISG17, Mark2, PPP2R1A-a, PPP2R1A-b, RUSC2 et WASH1 est indicative de l'affection de l'articulation du grasset.
10. Procédé ou essai *in vitro* selon la revendication 8 ou 9, **caractérisé en ce que** les taux d'expression d'au moins les marqueurs d'une des combinaisons de marqueurs suivantes sont mesurés : Foxl1 et WASH1 ; ou Foxl1 et PPP2R1A-a ; ou Foxl1 et PPP2R1A-b.
11. Procédé *in vitro* selon l'une quelconque des revendications 1 à 10 **caractérisé en ce que** les taux d'expression des marqueurs sont déterminés en mesurant l'ARNm du marqueur correspondant.
12. Procédé *in vitro* selon l'une quelconque des revendications 1 à 11 **caractérisé en ce que** les échantillons sont des échantillons de sang.
13. Utilisation d'un kit dans un procédé pour le diagnostic de l'ostéochondrose ou la prédiction de la probabilité de son apparition chez un cheval qui n'est pas âgé de plus de 12 mois, où le taux d'expression d'un marqueur dans un échantillon obtenu à partir dudit cheval est mesuré, et ledit taux d'expression est comparé au taux d'expression dudit marqueur mesuré dans un échantillon obtenu à partir d'un ou plusieurs chevaux non affectés par l'ostéochondrose, où le kit comprend au moins un agent, qui se lie spécifiquement au produit du gène du marqueur respectif et qui peut être utilisé pour déterminer le taux d'expression dudit marqueur, où le marqueur est ApoB- 3G ; où le kit comprend facultativement un ou des agent(s) additionnel(s) pour mesurer le taux d'expression d'un ou plusieurs marqueurs additionnels et/ou pour mesurer les taux d'expression d'un ou plusieurs gènes domestiques.
14. Utilisation selon la revendication 13, dans laquelle le kit comprend en outre
 - a) un ou des agent(s) additionnel(s) chacun pour mesurer le taux d'expression d'un marqueur choisi dans la liste constituée de Dsh1, Foxl1, Hp, ISG17, Mark2, PPP2R1A-a, PPP2R1A-b, RUSC2 et WASH1, où chaque agent additionnel se lie spécifiquement au produit du gène du marqueur respectif et qui peut être utilisé pour déterminer le taux d'expression du marqueur respectif ;
 - et/ou
 - b) un ou des agent(s) additionnel(s) pour mesurer le taux d'expression d'un gène domestique choisi dans la liste constituée de Axin1, CtBP1 et CD44, où chaque agent additionnel se lie spécifiquement au produit génique du gène domestique respectif et peut être utilisé pour déterminer le taux d'expression du gène domestique respectif.
15. Utilisation selon la revendication 13 ou 14, dans laquelle chaque agent est un ensemble d'amorces oligonucléotidiques comprenant une amorce sens ayant une longueur de 10 à 40 nucléotides qui possède au moins 70 % d'identité de séquence avec une séquence continue de la même longueur choisie parmi la séquence d'ADN du

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marqueur ou gène domestique respectif (SEQ ID NO: 1 à 13), et
soit une amorce antisens ayant une longueur de 10 à 40 nucléotides qui possède au moins 70 % d'identité de
séquence avec une séquence continue de la même longueur choisie parmi la séquence complémentaire de la
séquence d'ADN du marqueur ou gène domestique respectif (SEQ ID NO: 1 à 13), ou une amorce antisens ayant
une longueur de 10 à 40 nucléotides qui possède au moins 70 % d'identité de séquence avec une séquence continue
de polyadénosine ou polythymidine de la même longueur.

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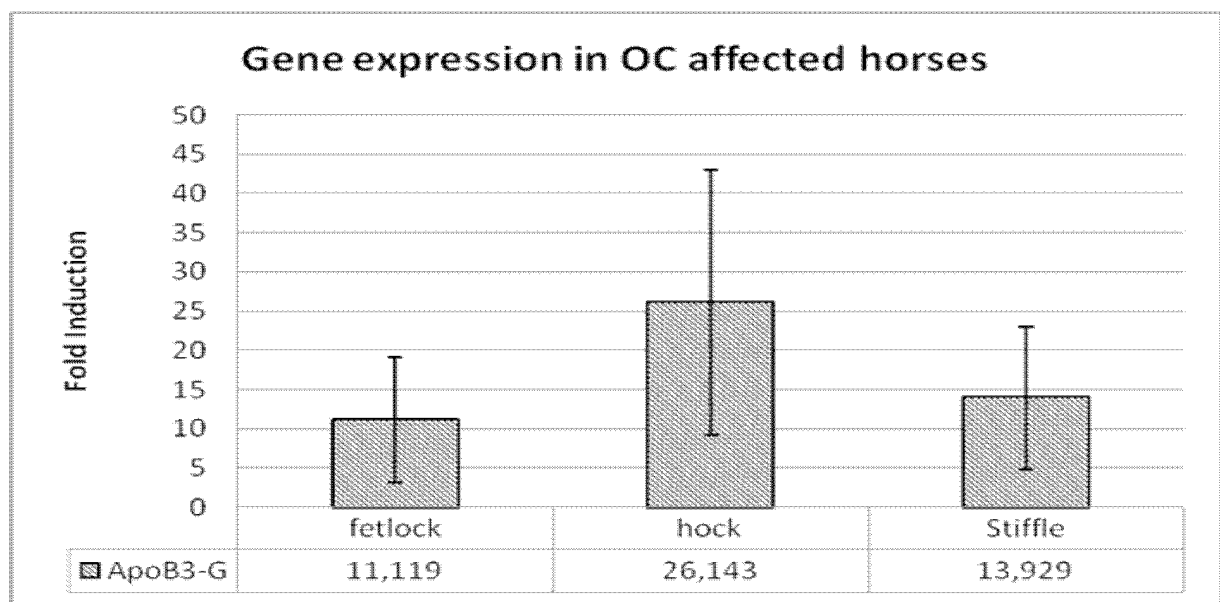
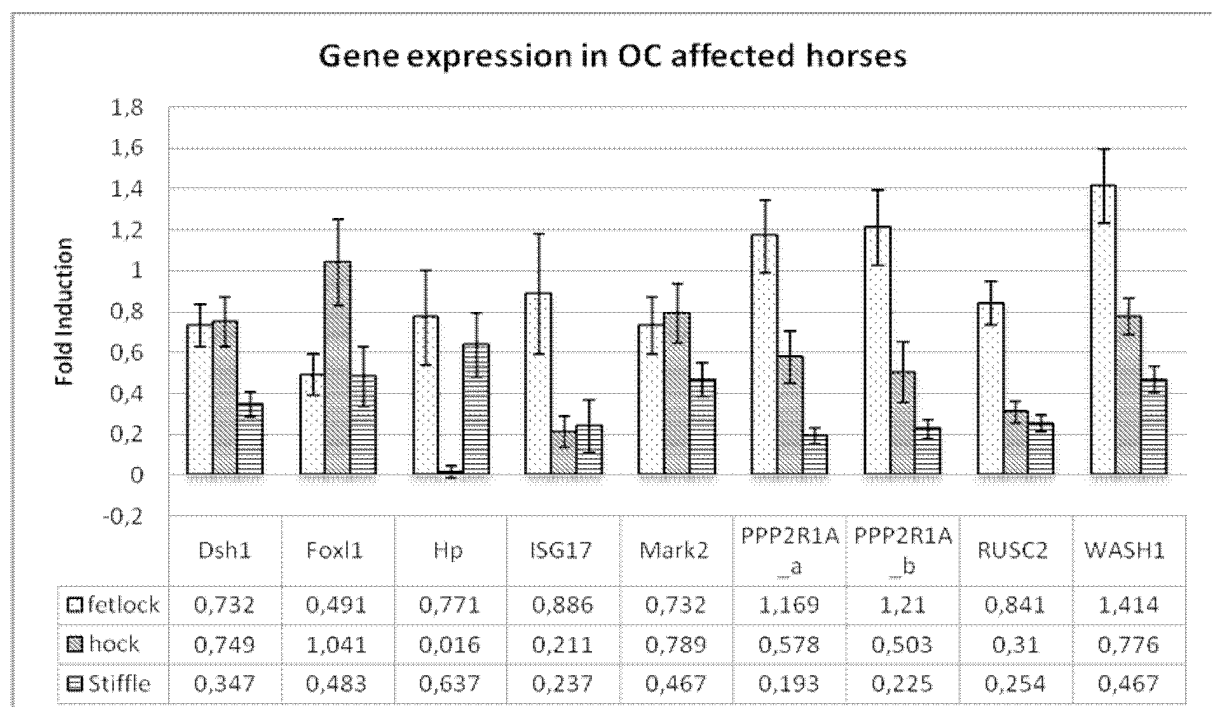


Fig. 1

**Fig. 2**

REFERENCES CITED IN THE DESCRIPTION

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